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(71) Applicant *(for all designated States except US)*: SAMJIN PHARMACEUTICAL CO., LTD. [KR/KR]; 338-8, Seokyo-dong, Mapo-ku, Seoul 121-210 (KR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CHO, Eui-Hwan [KR/KR]; 105-101, Hyundai Apartment, Kaepo 1-dong, Kangnam-ku, Seoul 135-241 (KR). CHUNG, Sun-Gan [KR/KR]; B-106, Seokyo Apartment, 344-1, Seokyo-dong, Mapo-ku, Seoul 121-210 (KR). KIM, Joong-Young [KR/KR]; 6-102, Sinmaetan Apartment, Maetan 3-dong, Paldal-ku, Suweon, Kungki-do 442-373 (KR). LEE, Sun-Hwan [KR/KR]; 105-403, Daelim Apartment, Dokkok-dong, Songtan, Kyungki-do 459-100 (KR). KWON, Ho-Seok [KR/KR]; 989-17, Inkyeo-dong, Paldal-ku, Suweon, Kyungki-do 442-070 (KR). KIM, Byung-Chul [KR/KR]; 102-412, Ajoo 1st Apartment, Jisan-dong, Songtan, Kyungki-do 459-110 (KR). KONG, Jae-Myeong [KR/KR]; 168-22, Yuljeon-dong, Jangan-ku, Suweon, Kyungki-do 440-320 (KR). LEE, Jae-Eung [KR/KR]; 390-3, Sinjang 2-dong, Hanam, Kyungki-do 465-032 (KR). KANG, Dong-Wook [KR/KR]; 5-2, Kangnam-dong, Jinju, Kyungsangnam-do 660-250 (KR).

(74) Agent: PARK, Sa, Ryong; 823-5, Yoksam-dong, Kangnam-ku, Seoul 135-080 (KR).

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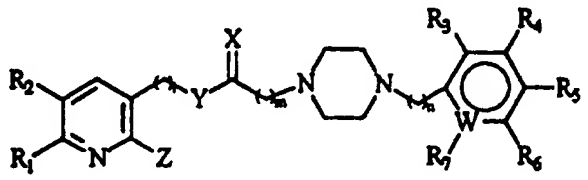
(54) Title: NEW PIPERAZINE DERIVATIVES AND METHODS FOR THE PREPARATION THEREOF AND COMPOSITIONS CONTAINING THE SAME

(57) Abstract

The present invention relates to novel compound of general formula (I) and acid addition salt thereof, wherein R_1 and R_2 are independently hydrogen, C_1-C_8 alkyl or optionally substituted C_3-C_6 membered cycloalkyl containing C_3-C_8; R_3, R_4, R_5, R_6 and R_7 are independently hydrogen, halogen, hydroxy, nitro, C_1-C_4 lower ester, C_1-C_4 lower alkyl, C_1-C_4 lower alkoxy, aryl, arylalkoxy or unsaturated amine; l is an integer of 0-7; m and n are independently an integer of 0-1; W is carbon or nitrogen; X is oxygen, sulfur, optionally substituted imine; Y is nitrogen or oxygen; and Z is hydrogen, C_1-C_8 alkoxy, aryloxy, C_1-C_4 alkylamine, cycloamine containing N_1-N_5 or oxo group. The present compounds of the above formula (I) have not only strong antitumor activities but lower toxicities, and accordingly are expected as novel antitumor agents.



(I)

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UZ	Uzbekistan
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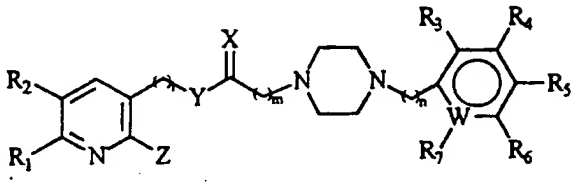
New piperazine derivatives and methods for the preparation thereof and compositions containing the same

The present invention relates to new piperazine derivatives of the general formula(I)



(I)

wherein R_1 and R_2 are independently hydrogen, C_1-C_8 alkyl or optionally substituted C_3-C_6 membered cycloalkyl containing C_3-C_8 ; R_3, R_4, R_5, R_6 and R_7 are independently hydrogen, halogen, hydroxy, nitro, C_1-C_4 lower ester, C_1-C_4 lower alkyl, C_1-C_4 lower alkoxy, aryl, arylalkoxy or unsaturated amine; l is an integer of 0-7; m and n are independently an integer of 0-1; W is carbon or nitrogen; X is oxygen, sulfur, optionally substituted imine; Y is nitrogen or oxygen; and Z is hydrogen, C_1-C_8 alkoxy, aryloxy, C_1-C_4 alkylamine, cycloamine containing N_1-N_5 or oxo group.

C_1-C_8 alkyl means straight or branch alkyl group such as methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, pentyl, iso-pentyl, hexyl, heptyl, octyl, 2-methyl-pentyl or the like.

C_1-C_4 lower alkyl means methyl, propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl or the like.

Optionally substituted 3-6 membered cycloalkyl containing C_3-C_8 means substituted or unsubstituted cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, substituted cyclopropyl, substituted cyclopentyl, substituted cyclohexyl or the like.

C_1-C_4 lower ester means a carboxyl group esterified by lower alkyl group.

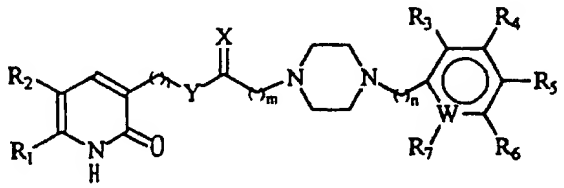
C_1-C_4 lower alkoxy means methoxy, ethoxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, tert-butyloxy group or the like.

Aryloxy means phenoxy, substituted phenoxy, naphthyloxy or substituted naphthyloxy or the like.

Cycloamine group containing N_1-N_5 means pyrrolidinyl, pyrrolinyl, imidazolyl,

imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, piperazinyl or the like.

The general formula(I) compound wherein Z is oxo has the structural formula(I') by tautomerism.



(I')

The present inventors had studied to find compounds having intensive antitumor activity for a long time. As the results, we finally found out the facts that the foresaid compounds of the general formula(I) and acid addition salts thereof have not only prominant antitumor activity but very low toxicity. Accordingly, the one object of the present invention is to provide the novel compounds of the general formula(I) and acid addition salts thereof having not only prominent antitumor activity but very low toxicity.

The other object of the present invention is to provide a process for the preparation of the compounds of general formula(I) and acid addition salts thereof.

The compounds of the present invention can be mixed with pharmaceutically acceptable vehicles by a known method to give pharmaceutical compositions and the pharmaceutical compositions can be used to prevent or treat various kinds of tumors of human beings or mammals.

Therefore, another object of the present invention is to provide pharmaceutical compositions containing the compounds of the general formula(I) and acid addition salts thereof as active ingredients.

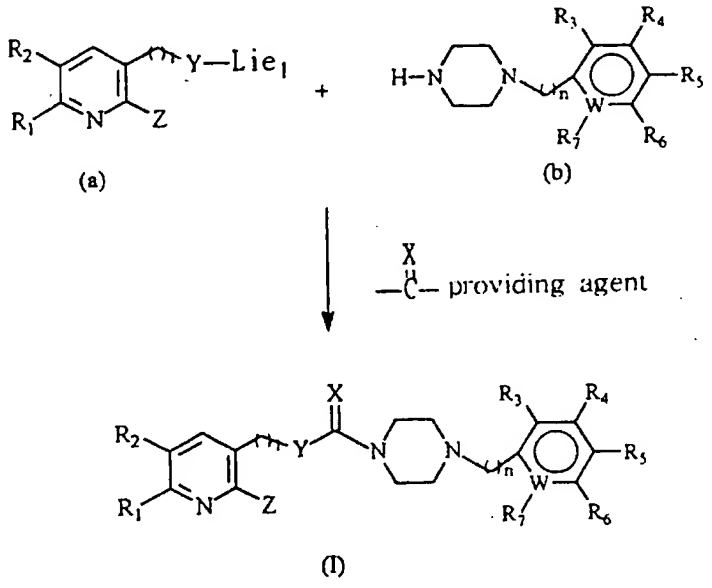
Acids which can be reacted with the compounds of the general formula(I) to form acid addition salts are pharmaceutically acceptable inorganic or organic acids such as hydrochloric acid, bromic acid, sulfuric acid, phosphoric acid, nitric acid, formic acid, acetic acid, propionic acid, succinic acid, citric acid, maleic acid, malonic acid, glycolic acid, lactic acid, glycine, alanine, valine, luecine, isoleucine, serine, cysteine, cystine, asparaginic acid, glutamic acid, lysine, arginine, tyrosine, proline, methane sulfonic acid, ethane sulfonic acid, benzene sulfonic acid, toluene sulfonic acid or the like.

Vehicles which can be used in the preparation of pharmaceutical compositions containing the compounds of the general formula(I) as active ingredient are sweetening agent, binding agent, dissolving agent, aids for dissolution, wetting agent, emulsifying agent, isotonic agent, adsorbent, degrading agent, antioxident, antiseptics, lubricating agent, filler and perfume or the like such as lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycine, sodium carboxy methyl cellulose, agar, talc, stearic acid, magnesium stearate, calcium stearate, magnesium aluminum silicate, starch, gelatine, tragacanth gum, methyl cellulose, glycine, silica, alginic acid, sodium alginate, water, ethanol, polyethylenglycol, polyvinyl pyrrolidone, sodium chloride, potassium chloride, orange essence, vanila aroma or the like.

Daily dosage of the compound of the general formula(I) may be varied depending on age, sex of patient and the degree of desease. Daily dosage is 1.0mg to 5,000mg and may be administered one to several times.

The compounds of the general formula(I) may be prepared by the following scheme 1.

Scheme 1



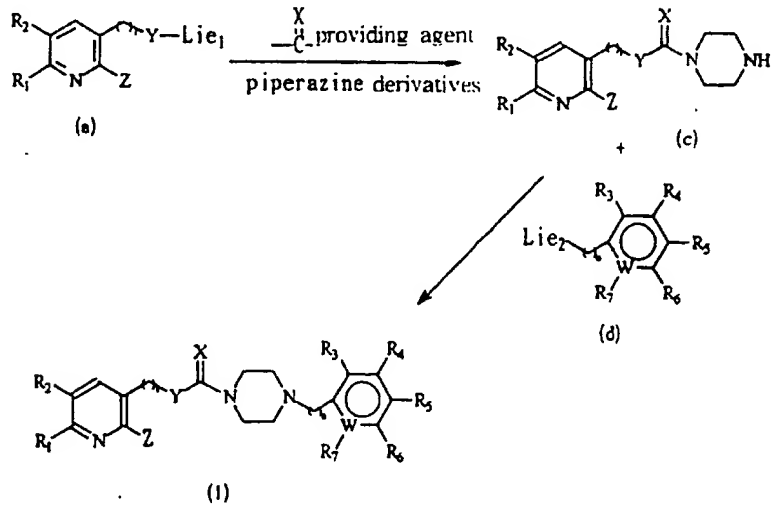
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, W, X, Y, Z, l and n are the same above and Lie_1 is a leaving group like hydrogen.

The compounds of the general formula(I) may be prepared by reacting a compound of the general formula(a) in the presense of -CX- group-providing agent with a compound of the general formula(b). -CX-group-providing agent comprises 1,1-carbonyldiimidazole, 1,1-carbonylthiodiimidazole, phosgene, thiophosgene, carbonyldiphenoxide, chlorophenoxyformate or the like. The reaction may be carried out in conventional organic solvent such as tetrahydrofuran, dichloromethane, acetonitrile or the like. And also the reaction is preferably carried out in the presence of scavenger such as conventional inorganic or organic base.

The reaction may be carried out between 3℃ and boiling point of the solvent used, preferably at 50℃-100℃ for 5 - 48 hours, preferably for 10 - 24 hours. Quantity of -CX-group-providing agent may be 1 - 1.5 equivalent, preferably 1-1.1 equivalent to the starting compound.

The compounds of the general formula(I) may be prepared by Scheme II.

Scheme II



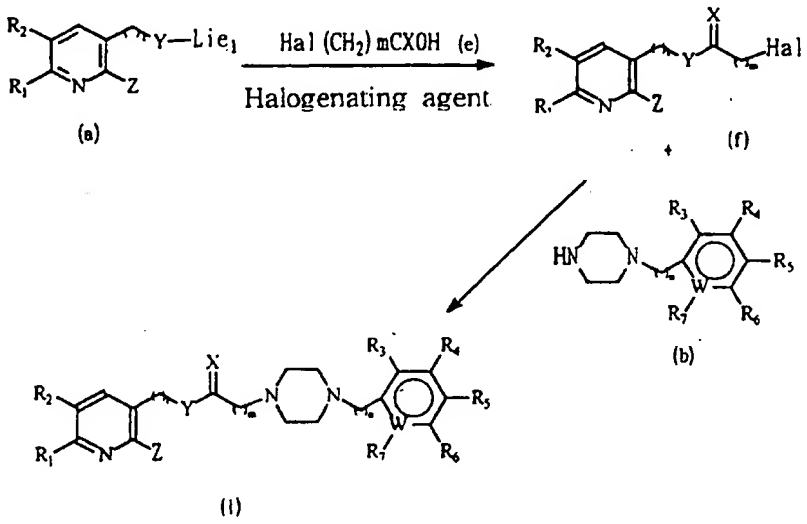
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, W, X, Y, Z, l, n, and Lie_1 are the same above and Lie_2 is halogen.

The compound of the general formula(c) may be prepared by reacting a

compound of the general formula(a) in the presence of -CX-providing agent with piperazine in a solvent such as tetrahydrofuran, acetonitrile or the like under the same reaction condition of Scheme I. And then the compound of the general formula(I) may be prepared by reacting the compound of the general formula(c) in a solvent such as tetrahydrofuran or the like with a compound of the general formula (d) at 25 - 80 ℃ for 30 min - 20 hours.

The compounds of the general formula(I) may be prepared by Scheme III.

Scheme III

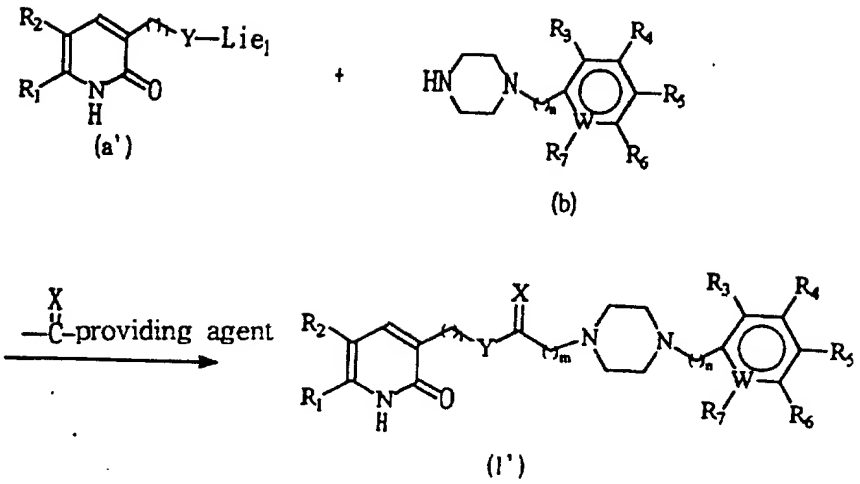


wherein, R_1, R_2, R_3, R_4, R_5, R_6, R_7, l, m, n, W, X, Y, Z and Lie_1 are the same above and Hal is halogen.

The compound of the general formula(f) may be prepared by reacting a compound of the general formula(a) with a compound of the general formula(e) and halogenating agent. And then the compound of the general formula(I) may be prepared by reacting the compound of the general formula(f) with a compound of the general formula(b).

The compound of the general formula(I') may be prepared by Scheme IV.

Scheme IV

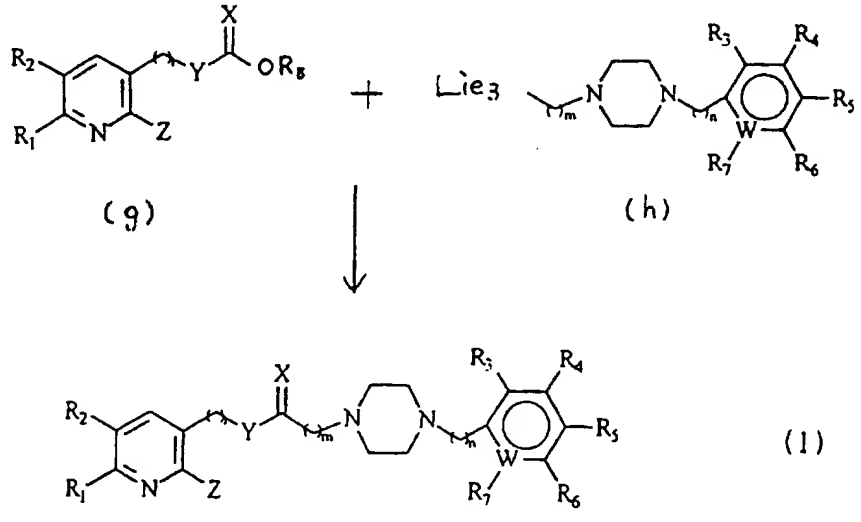


wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, l, m, n, W, X, Y, Z, and Lie_1 are the same above.

The compound of the general formula(I') may be prepared by reacting a compound of the general formula(a') in the presence of CX-providing agent in a solvent like tetrahydrofuran or the like with a compound of the general formula (b) at ambient temperature for 30 min ~ 5 hours.

The compounds of the general formula(I) may be prepared by Scheme V.

Scheme V



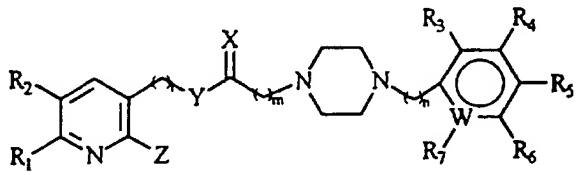
wherein, R_1, R_2, R_3, R_4, R_4, R_5, R_6, R_7, l, m, n, W, X, Y, Z are the same above and R_8 is C_1 - C_5 alkyl or aryl group, Lie_3 is a leaving group like hydrogen. The compound of general formula(g) and the compound of general formula(h) may be prepared by condensing agent.

In the above reactions, if any acid material is formed, any basic material is preferably added as scavenger in order to eleminating the acid material from the reaction phase. Such basic material may be alkali metal hydroxide, alkali earth metal hydroxide, alkali metal oxide, alkali earth metal oxide, alkali metal carbonate, alkali earth metal carbonate, alkali metal hydrogen carbonate, alkali earth metal hydrogen carbonate such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, calcium oxide, magnesium oxide, potassium carbonate, sodium carbonate, calcium carbonate, magnesium carbonate, magnesium bicarbonate, sodium bicarbonate. calcium bicabonate or the like and organic amines.

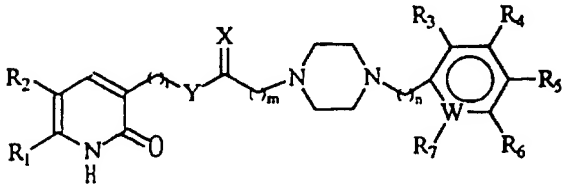
The compound of the general formula(a) is described in prior art (J. Med. Chem., 1992, 35, 3784, 3792) or may be prepared in a similar method to the art.

EXAMPLES:

The compounds of the general formula(I) and (I') are prepared by the following examples.



(I)



(I')

wherein R_1, R_2, R_3, R_4, R_5 , R_6, R_7, l, m, n, W, X, Y, Z are the same above.

ex. no	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X	Y	Z	W	l	m	n
												(l,m,n=integer)		
1	Me	Et	OMe	H	H	H	H	O	NH	OMe	C	0	0	0
2	Me	Et	H	H	H	H	H	O	NH	OMe	C	0	0	0
3	Me	Et	H	H	OMe	H	H	O	NH	OMe	C	0	0	0
4	Me	Et	H	OMe	OMe	H	H	O	NH	OMe	C	0	0	0
5	Me	Et	OMe	H	OMe	H	H	O	NH	OMe	C	0	0	0
6	Me	Et	H	OMe	H	OMe	H	O	NH	OMe	C	0	0	0
7	Me	Et	H	OMe	OMe	OMe	H	O	NH	OMe	C	0	0	0
8	Me	Et	OEt	H	H	H	H	O	NH	OMe	C	0	0	0
9	Me	Et	OPh	H	H	H	H	O	NH	OMe	C	0	0	0
10	Me	Et	H	OPh	H	H	H	O	NH	OMe	C	0	0	0
11	Me	Et	F	H	H	H	H	O	NH	OMe	C	0	0	0
12	Me	Et	H	H	F	H	H	O	NH	OMe	C	0	0	0
13	Me	Et	H	F	H	F	H	O	NH	OMe	C	0	0	0
14	Me	Et	H	CF_3	H	H	H	O	NH	OMe	C	0	0	0
15	Me	Et	Cl	H	H	H	H	O	NH	OMe	C	0	0	0

ex. no	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X	Y	Z	W	l	m	n
												(l,m,n=integer)		
16	Me	Et	H	Cl	H	H	H	O	NH	OMe	C	0	0	0
17	Me	Et	Cl	H	H	H	Cl	O	NH	OMe	C	0	0	0
18	Me	Et	H	Cl	H	Cl	H	O	NH	OMe	C	0	0	0
19	Me	Et	Cl	H	Cl	H	H	O	NH	OMe	C	0	0	0
20	Me	Et	Cl	H	Cl	H	Cl	O	NH	OMe	C	0	0	0
21	Me	Et	Br	H	H	H	H	O	NH	OMe	C	0	0	0
22	Me	Et	H	Br	H	H	H	O	NH	OMe	C	0	0	0
23	Me	Et	H	H	Br	H	H	O	NH	OMe	C	0	0	0
24	Me	Et	Br	H	Br	H	H	O	NH	OMe	C	0	0	0
25	Me	Et	Br	H	H	Br	H	O	NH	OMe	C	0	0	0
26	Me	Et	Me	H	H	H	H	O	NH	OMe	C	0	0	0
27	Me	Et	H	H	Me	H	H	O	NH	OMe	C	0	0	0
28	Me	Et	Me	Me	H	H	H	O	NH	OMe	C	0	0	0
29	Me	Et	H	Me	H	Me	H	O	NH	OMe	C	0	0	0
30	Me	Et	Me	H	H	H	Me	O	NH	OMe	C	0	0	0

ex. no	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X	Y	Z	W	l	m	n
												(l,m,n=integer)		
31	Me	Et	H	H	i-Pr	H	H	O	NH	OMe	C	0	0	0
32	Me	Et	i-Pr	H	H	H	H	O	NH	OMe	C	0	0	0
33	Me	Et	H	H	n-Bu	H	H	O	NH	OMe	C	0	0	0
34	Me	Et	H	H	Ac	H	H	O	NH	OMe	C	0	0	0
35	Me	Et	Ph	H	H	H	H	O	NH	OMe	C	0	0	0
36	Me	Et	H	H	Ph	H	H	O	NH	OMe	C	0	0	0
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39	Me	Et	H	H	OH	H	H	O	NH	OMe	C	0	0	0
40	Me	Et	H	H	OAc	H	H	O	NH	OMe	C	0	0	0
41	Me	Et	H	OAc	H	H	H	O	NH	OMe	C	0	0	0
42	Me	Et	H	H	NO_2	H	H	O	NH	OMe	C	0	0	0
43	Me	Et	$NHCH_3$	H	H	H	H	O	NH	OMe	C	0	0	0
44	Me	Et	H	H	H	-benzo-		O	NH	OMe	C	0	0	0
45	Me	Et	H	H	H	-naphtho-		O	NH	OMe	C	0	0	0

ex. no	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X	Y	Z	W	l	m	n
												(l,m,n=integer)		
46	Me	Et	OMe	H	H	H	Me	O	NH	OMe	C	0	0	0
47	Me	Et	OMe	H	H	Me	H	O	NH	OMe	C	0	0	0
48	Me	Et	Me	H	H	OMe	H	O	NH	OMe	C	0	0	0
49	Me	Et	OMe	H	H	Cl	H	O	NH	OMe	C	0	0	0
50	Me	Et	Cl	H	H	OMe	H	O	NH	OMe	C	0	0	0
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53	Me	Et	H	OAc	OMe	H	H	O	NH	OMe	C	0	0	0
54	Me	Et	OMe	H	H	Ph	H	O	NH	OMe	C	0	0	0
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56	Me	Et	OH	H	H	H	Me	O	NH	OMe	C	0	0	0
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58	Me	Et	Me	H	H	Cl	H	O	NH	OMe	C	0	0	0
59	Me	Et	H	Cl	F	H	H	O	NH	OMe	C	0	0	0
60	Me	Et	OMe	H	H	H	H	O	NH	OMe	C	1	0	0

ex. no	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X	Y	Z	W	l	m	n
												(l,m,n=integer)		
61	Me	Et	F	H	H	H	H	O	NH	OMe	C	1	0	0
62	Me	Et	H	H	F	H	H	O	NH	OMe	C	1	0	0
63	Me	Et	H	Cl	H	H	H	O	NH	OMe	C	1	0	0
64	Me	Et	H	H	F	H	H	O	NH	OMe	C	2	0	0
65	Me	Et	OMe	H	H	H	H	O	NH	OMe	C	2	0	0
66	Me	Et	OMe	H	H	H	H	O	NH	OMe	C	3	0	0
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69	Me	Et	OMe	H	H	H	H	O	NH	OMe	C	0	1	0
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71	Me	Et	F	H	H	H	H	O	NH	OMe	C	0	1	0
72	Me	Et	H	H	H	H	H	O	NH	OMe	C	0	0	1
73	Me	Et	H	H	OMe	H	H	O	NH	OMe	C	0	0	1
74	Me	Et	OMe	H	H	H	H	O	NH	OMe	C	0	0	1
75	Me	Et	H	H	F	H	H	O	NH	OMe	C	0	0	1

ex. no	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X	Y	Z	W	l	m	n
												(l,m,n=integer)		
76	Me	Et	OMe	H	H	H	H	O	NH	OEt	C	0	0	0
77	Me	Et	F	H	H	H	H	O	NH	OEt	C	0	0	0
78	Me	Et	H	Cl	H	H	H	O	NH	OEt	C	0	0	0
79	Me	Et	OEt	H	H	H	H	O	NH	OEt	C	0	0	0
80	Me	Et	OMe	H	H	H	H	O	NH	OPh	C	0	0	0
81	Me	Et	H	Cl	H	H	H	O	NH	OPh	C	0	0	0
82	Me	Et	H	OAc	H	H	H	O	NH	OPh	C	0	0	0
83	Me	Et	F	H	H	H	H	O	NH	OPh	C	0	0	0
84	Me	Et	H	Me	H	Me	H	O	NH	OPh	C	0	0	0
85	Me	Et	H	OMe	H	OMe	H	O	NH	OPh	C	0	0	0
86	Me	Et	H	Cl	H	Cl	H	O	NH	OPh	C	0	0	0
87	Me	Et	H	OH	OMe	H	H	O	NH	OPh	C	0	0	0
88	Me	Et	H	OH	H	H	H	O	NH	OPh	C	0	0	0
89	Me	Et	OMe	H	H	H	H	O	NH	$NHCH_3$	C	0	0	0
90	Me	Et	H	OMe	H	OMe	H	O	NH	$NHCH_3$	C	0	0	0

ex. no	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X	Y	Z	W	l	m	n
												(l,m,n=integer)		
91	Me	Et	H	Cl	H	H	H	O	NH	$NHCH_3$	C	0	0	0
92	Me	Et	OMe	H	H	H	H	O	NH	H	C	0	0	0
93	Me	Et	H	OMe	H	OMe	H	O	NH	H	C	0	0	0
94	Me	Et	H	Cl	H	H	H	O	NH	piperazine	C	0	0	0
95	Me	Et	H	Cl	H	H	H	O	NH	piperazine -Boc	C	0	0	0
96	Me	Et	OMe	H	H	H	H	O	NH	piperazine -Boc	C	0	0	0
97	Me	Et	OMe	H	H	H	H	S	NH	OMe	C	0	0	0
98	Me	Et	H	Cl	H	H	H	S	NH	OMe	C	0	0	0
99	Me	Et	F	H	H	H	H	S	NH	OMe	C	0	0	0
100	Me	Et	H	OMe	H	OMe	H	S	NH	OMe	C	0	0	0
101	Me	Et	H	Cl	H	Cl	H	S	NH	OMe	C	0	0	0
102	Me	Et	OMe	H	H	H	H	O	O	OMe	C	0	0	0
103	Me	Et	H	Cl	H	H	H	O	O	OMe	C	0	0	0
104	Me	Et	H	OMe	H	OMe	H	O	O	OMe	C	0	0	0
105	Me	Et	OMe	H	H	H	H	O	O	OMe	C	1	0	0

ex. no	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X	Y	Z	W	l	m	n
												(l,m,n=integer)		
106	Me	Et	H	Cl	H	H	H	O	O	OMe	C	1	0	0
107	Me	Me	H	H	H	H	H	O	NH	OMe	C	0	0	0
108	Me	Me	OMe	H	H	H	H	O	NH	OMe	C	0	0	0
109	Me	Me	H	Cl	H	H	H	O	NH	OMe	C	0	0	0
110	Me	Me	F	H	H	H	H	O	NH	OMe	C	0	0	0
111	Me	Me	H	F	H	F	H	O	NH	OMe	C	0	0	0
112	Me	Me	OH	H	H	H	H	O	NH	OMe	C	0	0	0
113	Me	Me	H	OH	H	H	H	O	NH	OMe	C	0	0	0
114	Me	Me	H	H	OH	H	H	O	NH	OMe	C	0	0	0
115	Me	Me	H	OAc	H	H	H	O	NH	OMe	C	0	0	0
116	Me	Me	H	H	OAc	H	H	O	NH	OMe	C	0	0	0
117	Me	Me	H	OAc	OMe	H	H	O	NH	OMe	C	0	0	0
118	Me	Me	H	OMe	H	OMe	H	O	NH	OMe	C	0	0	0
119	Me	Me	Me	Me	H	H	H	O	NH	OMe	C	0	0	0
120	Me	Me	H	Me	H	Me	H	O	NH	OMe	C	0	0	0

ex. no	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X	Y	Z	W	l	m	n
												(l,m,n=integer)		
121	Me	Me	Me	H	H	OMe	H	O	NH	OMe	C	0	0	0
122	Me	Me	OH	H	Me	H	H	O	NH	OMe	C	0	0	0
123	Me	Me	H	OH	OMe	H	H	O	NH	OMe	C	0	0	0
124	Me	Me	H	H	H	-benzo-		O	NH	OMe	C	0	0	0
125	Me	Me	H	H	H	-naphtho-		O	NH	OMe	C	0	0	0
126	Me	Me	H	Cl	H	H	H	S	NH	OMe	C	0	0	0
127	Me	Me	H	Cl	H	Cl	H	S	NH	OMe	C	0	0	0
128	Me	Me	OMe	H	H	H	H	S	NH	OMe	C	0	0	0
129	Me	Me	H	OMe	H	OMe	H	S	NH	OMe	C	0	0	0
130	$-(CH_2)_3-$		OMe	H	H	H	H	O	NH	OMe	C	0	0	0
131	$-(CH_2)_3-$		H	Cl	H	H	H	O	NH	OMe	C	0	0	0
132	$-(CH_2)_3-$		F	H	H	H	H	O	NH	OMe	C	0	0	0
133	$-(CH_2)_4-$		OMe	H	H	H	H	O	NH	OMe	C	0	0	0
134	$-(CH_2)_4-$		H	Cl	H	H	H	O	NH	OMe	C	0	0	0
135	$-(CH_2)_4-$		F	H	H	H	H	O	NH	OMe	C	0	0	0

ex. no	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X	Y	Z	W	l	m	n
												(l,m,n=integer)		
136	Me	i-Pr	OMe	H	H	H	H	O	NH	OMe	C	0	0	0
137	Me	i-Pr	H	Cl	H	H	H	O	NH	OMe	C	0	0	0
138	Me	i-Pr	F	H	H	H	H	O	NH	OMe	C	0	0	0
139	H	H	H	H	H	H	H	O	NH	OMe	C	0	0	0
140	H	H	OMe	H	H	H	H	O	NH	OMe	C	0	0	0
141	H	H	H	H	OMe	H	H	O	NH	OMe	C	0	0	0
142	H	H	H	Cl	H	H	H	O	NH	OMe	C	0	0	0
143	Me	Et	$NHCH_2CCH$	H	H	H	H	O	NH	OMe	N	0	0	0
144	Me	Et	$NHCH_2CCH$	H	H	H	H	O	NH	OMe	N	1	0	0
145	Me	Et	$NHCH_2CCH$	H	H	H	H	O	NH	=O	N	1	0	0
146	Me	Et	$N(CH_2Ph)_2$	H	H	H	H	O	NH	=O	N	1	0	0
147	Me	i-Pr	NHEt	H	H	H	H	O	NH	=O	N	1	0	0
148	Me	Et	OMe	H	H	H	H	O	NH	OMe	C	0	0 HCl salt	0
149	Me	Et	H	Cl	H	H	H	O	NH	OMe	C	0	0 HCl salt	0

Example 1

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate(0.29g, 1.0mmol) and 1-(2-methoxyphenyl)piperazine(0.19g, 1.0mmol) were dissolved in tetrahydrofuran(10ml) and DBU(0.15g, 1.0mol) was added thereto and the mixture was stirred at room temperature for 2 hours. Then, the reaction mixture was concentrated and chromatographed to obtain 0.33g of the titled compound.

yield: 89 %

^{1}H-NMR(500MHZ, $CDCl_3$): δ 1.17(3H,t,J=7.5Hz), 2.37(3H,s), 2.55(2H,q,J=7.5Hz), 3.11(4H,t,J=4.6Hz), 3.69(4H,t,J=5.0Hz), 3.88(1H,s), 3.98(3H,s), 6.89(1H,s), 6.94(3H,m), 7.05(1H,m), 8.21(1H,s).

Elemental Analysis: $C_{21}H_{28}N_4O_3$: Calc., C,65.60, H,7.34, N,14.57.
Found, C,66.10, H,7.25, N,14.57.

Example 2

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-phenylpiperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-phenylpiperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield: 86 %

Example 3

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-methoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(4-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield: 78 %

Example 4

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,4-dimethoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and

1-(3,4-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:69 %

Example 5
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,4-dimethoxyphenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2,4-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield: 77 %

Example 6
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield : 82 %

Example 7
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,4,5-trimethoxyphenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3,4,5-trimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield : 52 %

Example 8
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-ethoxyphenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-ethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield : 78 %

Example 9

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-phenoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-phenoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 69 %

Example 10

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-phenoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-phenoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 72 %

Example 11

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-fluorophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-fluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 67 %

Example 12

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-fluorophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(4-fluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 81 %

Example 13

1-[(5-ethyl-2-methoxy-6-methylpyridine-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 69 %

Example 14

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(α , α , α -trifluoro-m-tolyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(α , α , α -triflouro-m-tolyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield: 67 %

Example 15

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-chlorophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :82 %

Example 16

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-chlorophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :84 %

Example 17

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,6-dichlorophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2,6-dichlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :80 %

Example 18

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :69 %

Example 19
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,4-dichlorophenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2,4-dichlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :72 %

Example 20
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,4,6-trichlorophenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2,4,6-trichlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :54 %

Example 21
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-bromophenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-bromophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :58 %

Example 22
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-bromophenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-bromophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :65 %

Example 23

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-bromophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(4-bromophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :64 %

Example 24

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,4-dibromophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2,4-dibromophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :68 %

Example 25

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,5-dibromophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2,5-dibromophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :66 %

Example 26

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-tolyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-tolyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :89 %

Example 27

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-methylphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(4-methylphenyl)piperazine were reacted by the same way with the example

1 to obtain the titled compound.
yield :87 %

Example 28

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,3-dimethylphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :82 %

Example 29

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :68 %

Example 30

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,6-dimethylphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2,6-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound

yield :80 %

Example 31

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-isopropylphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(4-isopropylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :68 %

Example 32

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-isopropylph-

enyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-isopropylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :65 %

Example 33

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-normalbutylphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(4-normalbutylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :57 %

Example 34

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-acetylphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(4-acetylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :67 %

Example 35

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-biphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-biphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :82 %

Example 36

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-biphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(4-biphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :81 %

Example 37

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-hydroxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-hydroxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :59 %

Example 38

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :63 %

Example 39

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-hydroxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(4-hydroxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :58 %

Example 40

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-acetoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :89 %

Example 41

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-acetoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and

1-(3-acetoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :87 %

Example 42
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-nitrophenyl) piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(4-nitrophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :70 %

Example 43
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-[(2-methylamino)phenyl]piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-[2-(methylamino)phenyl]piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :59 %

Example 44
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(1-naphthyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(1-naphthyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :63 %

Example 45
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(1-anthryl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(1-anthryl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :57 %

Example 46

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxy-6-methylphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-methoxy-6-methylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :67 %

Example 47

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxy-5-methylphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-methoxy-5-phenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :62 %

Example 48

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(5-methoxy-2-methylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :66 %

Example 49

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(5-chloro-2-methoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(5-chloro-2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :69 %

Example 50

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-chloro-5-methoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-chloro-5-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :70 %

Example 51

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-chloro-4-methoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-chloro-4-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :62 %

Example 52

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-hydroxy-4-methoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-hydroxy-4-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :59 %

Example 53

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-acetoxy-4-methoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-acetoxy-4-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :62 %

Example 54

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-[(2-methoxy-5-phenyl)phenyl]piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-[(2-methoxy-5-phenyl)phenyl]piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :67 %

Example 55

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-hydroxy-2-methylphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-hydroxy-2-methylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :54 %

Example 56
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-hydroxy-6-methylphenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-hydroxy-6-methylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :57 %

Example 57
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-hydroxy-4-methylphenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-hydroxy-4-methylphenyl)piperazine were reacted by the same way with example 1 to obtain the titled compound.
yield :52 %

Example 58
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(5-chloro-2-methylphenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(5-chloro-2-methylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :63 %

Example 59
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-chloro-4-fluorophenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-fluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :65 %

Example 60

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :69 %

Example 61

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-chlorophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :72 %

Example 62

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)methylaminocarbonyl]-4-(4-fluorophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(4-fluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :63 %

Example 63

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)methylaminocarbonyl]-4-(3-chlorophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield :68 %

Example 64

1-{[(5-ethyl-2-methoxy-6-methylpyridin-3-yl]ethylaminocarbonyl}-4-(4-fluorophenyl)piperazine:

Phenyl-N-[2-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)ethyl]carbamate and 1-(4-fluorophenyl)piperazine were reacted by the same way with the example

1 to obtain the titled compound.
yield :65 %

Example 65
1-{[2-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)ethyl]aminocarbonyl}-4-(2-methoxyphenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :63 %

Example 66
1-{[3-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)propyl]aminocarbonyl}-4-(2-methoxyphenyl)piperazine:
Phenyl-N-[3-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)propyl]carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :67 %

Example 67
1-{[5-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)pentyl]aminocarbonyl}-4-(2-methoxyphenyl)piperazine:
Phenyl-N-[5-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)pentyl]carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :52 %

Example 68
1-{[6-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)heptyl]aminocarbonyl}-4-(2-methoxyphenyl)piperazine:
Phenyl-N-[6-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)heptyl]carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield :49 %

Example 69
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]methyl-4-(2-met-

hoxyphenyl)piperazine:

a) N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)chloroacetamide:

After chloroacetic acid (1.35 g, 14.3 mmol) were dissolved into 20 ml of tetrahydrofuran, added 1,1-carbonyldiimidazole(2.32g, 14.3mmol), stirred at room temperature for 1 hour, 3-amino-5-ethyl-2-methoxy-6-methylpyridine (2.0g, 13.0mmol) were added. After the reaction mixture were stirred for 2 hours, the mixture of reaction were concentrated, purified by column chromatography to obtain 2.20g of the titled compound.

yield:73.3%

^{1}H-NMR(500MHz, $CDCl_3$); δ 1.17(3H,t), 2.39(5H,m), 3.99(3H,s), 4.17(2H,s), 8.62(1H,s)

b) 1-[(5-ethyl-2-methoxy-6-methylpyridine-3-yl)aminocarbonyl]methyl-4-(2-methoxyphenyl)piperazine:

After N-(5-ethyl-2-methoxy-6-metylpyridine-3-yl)chloroacetamide(0.10g, 0.43mmol) and 1-(2-methoxyphenyl)piperazine(0.0091g, 0.47mmol) were dissolved into tetrahydrofuran(5ml) and was added DBU(0.060g, 0.43mmol), the reaction mixtures were stirred at room temperature for 2 hours. After the product of reaction were concentrated, separated by column chromatography to obtain 0.12g of the titled compound.

yield:70%

Example 70.

1-[(5-ethyl-2-methoxy-6-methylpyridine-3-yl)aminocarbonyl]methyl-4-(3-chlorophenyl)piperazine:

N-(5-ethyl-2-methoxy-6-methylpyridine-3-yl)chloroacetamide and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 69 to obtain the titled compound.

yield:68%

Example 71.

1-[(5-ethyl-2-methoxy-6-methylpyridine-3-yl)aminocarbonyl]methyl-4-(2-fluorophenyl)piperazine:

N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)chloroacetamide and 1-(3-fluorophenyl)piperazine were reacted by the same way with the example 69 to obtain the titled compound.

yield:68%

Example 72.

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-benzylpiperazine:

a) 1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-methoxy benzyl)piperazine.

After 3-amino-5-ethyl-2-methoxy-6-methylpyridine(1.06g, 6.35mmol) was dissolved in 20ml of tetrahydrofuran, 1,1-carbonyldiimidazole(1.08g, 6.67mmol) was added thereto. The mixture of reaction was stirred at room temperature for half hour and then benzylpiperazine(1.12g, 6.35mmol) was added. After the reaction mixture was stirred for 2 hours, the reaction mixture was concentrated and chromatographed to obtain 1.78g of the oil phase of the titled compound.

yield:76%

^{1}H-NMR(500MHz,$CDCl_3$): δ 1.16(3H,t), 2.36(3H,s), 2.48(4H,t), 3.42(4H,s), 3.54(2H,t), 3.95(H,s), 7.31(5H,s), 8.19(1H,s)

b) 1-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl piperazine:

After 1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-benzyl piperazine (1.71g, 4.61mmol) was added the solution of 30ml of ethanol and 10ml of glacial acetic acid in the presence of 5% Pd/C, the reaction mixture were stirred under hydrogen gas(40 psi) for 4 hours and extracted with dichloromethane. The mixture was dried with anhydrous magnesium sulfate, filtrated, concentrated and chromatographed to obtain 1.2 g of white solid of the titled compound.

yield:93%

^{1}H-NMR(500MHz, $CDCl_3$) : δ 1.16(3H,s), 2.35(3H,s), 2.48(2H,q), 2.94(4H,t), 3.52(4H,t), 8.02(1H,s)

c) 1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-benzylpiperazine:

After 1-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl piperazine (0.16g, 0.57mmol) and benzylchloride(0.076g, 0.60mmol) were added in DMF 5ml in the presence of $NaHCO_3$(0.114g, 1.36mmol), the reaction mixtures were stirred in 90℃ for 4 hours. The reaction solution was cooled at room temperature and the reaction mixture was extracted with dichloromethane and chromatographed to obtain 0.082gm of the titled compound.

yield:39%

^{1}H-NMR(500MHz, $CDCl_3$): δ 1.16(3H,t), 2.36(3H,s), 2.48(4H,t), 3.42(4H,t), 3.54(2H,s), 3.95(5H,s), 7.31(5H,s), 8.19(1H,s)

Example 73.

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-methoxybenzyl)piperazine:

1-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonylpiperazine and 4-methoxybenzylchloride were reacted by the same way with the example 72 to obtain the titled compound.

yield:42%

Example 74.

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxybenzyl)piperazine:

1-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonylpipeazine and 2-methoxybenzylchloride were reacted by the same way with the example 72 to obtain the titled compound.

yield:47%

Example 75.

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(4-fluorobenzyl)piperazine:

1-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonylpipeazine and 4-fluorobenzylchloride were reacted by the same way with the example 72 to obtain the titled compound.

yield:52%

Example 76.

1-[(2-ethoxy-5-ethyl-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

Phenyl-N-(2-ethoxy-5-ethyl-6-methylpyridin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:82%

Example 77.

1-[(2-ethoxy-5-ethyl-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-fluorophenyl)piperazine:

Phenyl-N-(2-ethoxy-5-ethyl-6-methylpyridin-3-yl)carbamate and

1-(2-fluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:87%

Example 78.
1-[(2-ethoxy-5-ethyl-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-chlorophenyl) piperazine:
Phenyl-N-(2-ethoxy-5-ethyl-6-methylpyridin-3-yl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:83%

Example 79.
1-[(2-ethoxy-5-ethyl-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-ethoxyphenyl) piperazin:
Phenyl-N-(2-ethoxy-5-ethyl-6-methylpyridin-3-yl)carbamate and 1-(2-ethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:79%

Example 80.
1-[(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:
Phenyl-N-(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:88%

Example 81.
1-[(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)aminocarbonyl]-4-(3-chlorophenyl)piperazine:
Phenyl-N-(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:85%

Example 82.

1-[(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)aminocarbonyl]-4-(3-acetoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)carbamate and 1-(3-acetoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:83%

Example 83.

1-[(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)aminocarbonyl]-4-(2-fluorophenyl)piperazine:

Phenyl-N-(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)carbamate and 1-(2-fluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:72%

Example 84.

1-[(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)aminocarbonyl]-4-(3,5-xylyl)piperazine:

Phenyl-N-(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)carbamate and 1-(3,5-xylyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:78%

Example 85.

1-[(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:75%

Example 86.

1-[(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl)piperazine:

Phenyl-N-(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)carbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:82%

Example 87.

1-[(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)aminocarbonyl]-4-(3-hydroxy-4-methoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)carbamate and 1-(3-hydroxy-4-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:69%

Example 88.

1-[(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine:

Phenyl-N-(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)carbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:72%

Example 89.

1-[(5-ethyl-6-methyl-2-methylaminopyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-6-methyl-2-methylaminopyridin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:73%

Example 90.

1-[(5-ethyl-6-methyl-2-methylaminopyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-6-methyl-2-methylaminopyridin-3-yl)carbamate and 1-(3,5-dimetoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:82%

Example 91.

1-[(5-ethyl-6-methyl-2-phenoxypyridin-3-yl)aminocarbonyl]-4-(3-chlorophenyl)piperazine:

Phenyl-N-(5-ethyl-6-methyl-2-methylaminopyridin-3-yl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:79%

Example 92.
1-[(5-ethyl-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:
Phenyl-N-(5-ethyl-6-methylpyridin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:80%

Example 93.
1-[(5-ethyl-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl-N-(5-ethyl-6-methylpyridin-3-yl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:85%

Example 94.
1-{[5-ethyl-6-methyl-2-(1-piperazinyl)pyridin-3-yl]aminocarbonyl}-4-(3-chlorophenyl)piperazine:
Phenyl-N-{[5-ethyl-6-methyl-2-(1-piperazinyl)pyridin-3-yl]carbamate and 4-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:87%

Example 95.
1-{[5-ethyl-6-methyl-2-(4-bocpiperazinyl)pyridin-3-yl]aminocarbonyl}-4-(3-chlorophenyl)piperazine:
Phenyl-N-{[5-ethyl-6-methyl-2-(4-boc-piperazinyl)pyridin-3-yl]carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:92%

Example 96.

1-{[5-ethyl-6-methyl-2-(4-boc-piperazinyl)pyridin-3-yl]aminocarbonyl}-4-(2-methoxyphenyl)piperazine:

Phenyl-N-{[5-ethyl-6-methyl-2-(4-boc-piperazinyl)pyridin-3-yl]carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:94%

Example 97.

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(2-methoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)thiocarbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:93%

Example 98.

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3-chlorophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)thiocarbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:88%

Example 99.

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(2-fluorophenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)thiocarbamate and 1-(2-fluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:82%

Example 100.

1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridine-3-yl)thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the

example 1 to obtain the titled compound.
yield:85%

Example 101
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dichlorophenyl)piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)thiocarbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:84%

Example 102.
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)oxycarbonyl]-4-(2-methoxyphenyl)piperazine:
Phenyl-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbonate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:72%

Example 103.
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)oxycarbonyl]-4-(3-chlorophenyl)piperzine:
Phenyl-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbonate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:74%

Example 104.
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)oxycarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbonate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:77%

Example 105.
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)methyloxycarbonyl]-4-(2-metho-

xyphenyl)piperazine:
Phenyl-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)methylcarbonate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:82%

Example 106.
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)methyloxycarbonyl]-4-(3-chlorophenyl)piperazine:
Phenyl-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)methylcarbonate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:79%

Example 107.
1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-phenylpiperazine:
Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-phenylpiperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:84%

Example 108.
1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:
Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:88%

Example 109.
1-[(5,6-dimethyl 2-methoxypyridin-3-yl)aminocarbonyl]-4-(3-chlorophenyl)piperazine:
Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:92%

Example 110.

1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-fluorophenyl)piperazine:

Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(2-fluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:79%

Example 111.

1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:87%

Example 112.

1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminothiocarbonyl]-4-(2-hydroxyphenyl)piperazine:

Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(2-hydroxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:85%

Example 113.

1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine:

Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:78%

Example 114.

1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(4-hydroxyphenyl)piperazine:

Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(4-hydroxyphenyl)piperazine were reacted by the same way with the

example 1 to obtain the titled compound.
yield:72%

Example 115.
1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3-acetoxyphenyl) piperazine:
Phenyl N (5,6 dimethyl 2 methoxypyridin 3 yl)carbamate and 1-(3-acetoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:92%

Example 116.
1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(4-acetoxyphenyl) piperazine:
Phenyl N (5,6 dimethyl 2 methoxypyridin 3 yl)carbamate and 1-(4-acetoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:89%

Example 117.
1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3-acetoxy-4-methoxyphenyl)piperazine:
Phenyl N (5,6 dimethyl 2 methoxypyridine 3 yl)carbamate and 1-(3-acetoxy-4-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:69%

Example 118.
1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:88%

Example 119.
1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2,3-xylyl)piperazine

Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(2,3-xylyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:72%

Example 120.
1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-xylyl)piperazine :
Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(3,5-xylyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:68%

Example 121.
1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2,5-xylyl)piperazine :
Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(2,5-xylyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:72%

Example 122.
1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-hydroxy-4-methylphenyl)piperazine:
Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(2-hydroxy-4-methylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:77%

Example 123.
1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3-hydroxy-4-methoxyphenyl)piperazine:
Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(3-hydroxy-4-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:69%

Example 124.

1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(1-naphthyl)piperazine:

Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(1-naphthyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:74%

Example 125.

1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(1-anthryl)piperazine:

Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(1-anthryl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:62%

Example 126.

1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminothiocarbonyl]-4-(3-chlorophenyl)piperazine:

Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)thiocarbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:69%

Example 127.

1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl)piperazine:

Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)thiocarbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:82%

Example 128.

1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxypheyl)piperazine:

Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)thiocarbamate and

1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:70%

Example 129.
1-[(5,6-dimethyl-2-methoxypyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:69%

Example 130.
1-[(2-methoxy-5,6,7-trihydro-1-pyrinden-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:
Phenyl-N-(2-methoxy-5,6,7-trihydro-1-pyrinden-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:64%

Example 131.
1-[(2-methoxy-5,6,7-trihydro-1-pyrinden-3-yl)aminocarbonyl]-4-(3-chlorophenyl)piperazine:
Phenyl-N-(2-methoxy-5,6,7-trihydro-1-pyrinden-3-yl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:63%

Example 132.
1-[(2-methoxy-5,6,7-trihydro-1-pyrinden-3-yl)aminocarbonyl]-4-(2-fluorophenyl)piperazine:
Phenyl-N-(2-methoxy-5,6,7-trihydro-1-pyrinden-3-yl)carbamate and 1-(2-fluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:59%

Example 133.

1-[(2-methoxy-5,6,7,8-tetrahydroisoquinolin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

Phenyl-N-(2-methoxy-5,6,7,8-tetrahydroisoquinolin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:64%

Example 134.

1-[(2-methoxy-5,6,7,8-tetrahydroisoquinolin-3-yl)aminocarbonyl]-4-(3-chlorophenyl)piperazine:

Phenyl-N-(2-methoxy-5,6,7,8-tetrahydroisoquinolin-3-yl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:69%

Example 135.

1-[(2-methoxy-5,6,7,8-tetrahydroisoquinolin-3-yl)aminocarbonyl]-4-(2-fluorophenyl)piperazine:

Phenyl-N-(2-methoxy-5,6,7,8-tetrahydroisoquinolin-3-yl)carbamate and 1-(2-fluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:70%

Example 136.

1-[(5-isopropyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

Phenyl-N-(5-isopropyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:64%

Example 137.

1-[(5-isopropyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-chlorophenyl)piperazine:

Phenyl-N-(5-isopropyl-2-methoxy-6-methylpyridine-3-yl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:63%

Example 138.

1-[(5-isopropyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-fluorophenyl)piperazine:

Phenyl-N-(5-isopropyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-fluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:59%

Example 139.

1-[(2-methoxypyridin-3-yl)aminocarbonyl]-4-phenylpiperazine:

Phenyl-N-(2-methoxypyridin-3-yl)carbamate and 1-phenylpiperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:88%

Example 140.

1-[(2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

Phenyl-N-(2-methoxypyridin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:86%

Example 141.

1-[(2-methoxypyridin-3-yl)aminocarbonyl]-4-(4-methoxyphenyl)piperazine:

Phenyl-N-(2-methoxypyridin-3-yl)carbamate and 1-(4-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:85%

Example 142.

1-[(2-methoxypyridin-3-yl)aminocarbonyl]-4-(3-chlorophenyl)piperazine:

Phenyl-N-(2-methoxypyridin-3-yl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield:72%

Example 143.
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-[(3-propargyl-amino)pyridin-2-yl]piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-[(3-propargylamino)pyridine-2-yl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:61%

Example 144.
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)methylaminocarbonyl]-4-[(3-propargylamino)pyridin-2-yl]piperazine:
Phenyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)methylcarbamate and 1-[(3-propargylamino)pyridin-2-yl]piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:74%

Example 145.
1-{[5-ethyl-6-methyl-2(1H)-pyridinon-3-yl]methylaminocarbonyl}-4-[(3-propa-rgylamino)pyridin-2-yl]piperazine:
Phenyl-N-[5-ethyl-6-methyl-2(1H)-pyridinon-3-yl]methylcarbamate and 1-[(3-propargylamino)pyridin-2-yl]piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:77%

Example 146.
1-{[5-ethyl-6-methyl-2(1H)-pyridinon-3-yl]methylaminocarbonyl}-4-[(3-dibenzylamino)pyridin-2-yl]piperazine:
Phenyl-N-[5-ethyl-6-methyl-2(1H)-pyridinon-3-yl]methylcarbamate and 1-[(3-dibenzylamino)pyridine-2-yl]piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield:65%

Example 147.
1-{[5-isopropyl-6-methyl-2(1H)-pyridinon-3-yl]methylaminocarbonyl}-4-[(3-ethylamino)pyridin-2-yl]piperazine:
Phenyl-N-[5-ethyl-6-methyl-2(1H)-pyridinon-3-yl]methylcarbamate and 1-[(3-ethylamino)pyridin-2-yl]piperazine were reacted by the same way with

the example 1 to obtain the titled compound.
yield:62%

Example 148.
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-[(2-methoxyphenyl)piperazine-2-yl]piperazine salt of hydrochloride:
After 1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine(5.0g, 13mmol) was dissolved in 400ml of diethylether, the mixture was saturated by hydrogen chloride gas at 0℃ and stirred for 30 minutes and purified to obtain the titled compound.
yield:98%

Example 149.
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-chlorophenyl)piperazine salt of hydrochloride:
1-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-chlorophenyl)piperazine was reacted by the same way with the example 148 to obtain the titled compound.
yield:98%

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
1	$C_{21}H_{28}N_4O_3$: theoretical, C, 65.60, H, 7.34, N, 14.57 experimental, C, 66.10, H, 7.25, N, 14.57	1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.11(4H, t, J=4.6Hz), 3.69(4H, t, J=5.0Hz), 3.88(1H, s), 3.98 (3H, s), 6.89(1H, s), 6.94(3H, m), 7.05 (1H, m), 8.21(1H, s).	115-118℃
2		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.26(4H, t, J=4.5Hz), 3.68(4H, t), 3.98(3H, s), 6.91(1H, s), 6.95(4H, m), 7.28(1H, m), 8.35(1H, s).	102-103℃
3		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=8.0Hz), 3.12(4H, t), 3.63 (4H, t), 3.78(3H, s), 3.97(3H, s), 6.85 (1H, s), 6.87(2H, m), 6.97(2H, m), 8.19(1H, s).	84-85℃
4		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.04(4H, t), 3.68 (4H, t), 3.79(3H, s), 3.86(3H, s), 3.97 (3H, s), 6.43(1H, d), 6.50(1H, s), 6.87 (1H, d), 6.92(1H, s), 8.21(1H, s).	116-119℃
5		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.14(4H, t), 3.68 (4H, t), 3.85(3H, s), 3.88(3H, s), 3.97 (3H, s), 6.49(1H, d), 6.60(1H, s), 6.82 (1H, d), 6.92(1H, s), 8.21(1H, s).	103-104℃
6	$C_{22}H_{30}N_4O_4$: theoretical, C, 63.75, H, 7.30, N, 13.52 experimental, C, 63.81, H, 7.31, N, 13.32	1.17(2H, q, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.27(4H, t), 3.74 (4H, t), 3.79(6H, s), 3.98(3H, s), 6.09 (1H, s), 6.16(2H, s), 6.90(1H, s), 8.19(1H, s)	126-127℃
7		1.16(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.20(4H, t, J=4.7Hz), 3.69(4H, t), 3.80(3H, s), 3.86(6H, s), 3.98(3H, s), 6.20(2H, s), 8.19(1H, s).	oil phase
8	$C_{22}H_{30}N_4O_3$: theoretical, C, 66.31, H, 7.59, N, 14.06 experimental, C, 66.13, H, 7.72, N, 13.78	1.17(3H, q, J=7.5Hz), 1.48(3H, t, J=6.95 Hz), 2.37(3H, s), 2.56(2H, q, J=7.5Hz), 3.14(4H, t, J=4.7Hz), 3.69(4H, t, J=4.6 Hz), 3.98(3H, s), 4.10(2H, q), 6.87(1H, s), 6.92(3H, m), 7.01(1H, m), 8.21(1H, s)	96-97℃

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
9		1.16(3H, t, J=7.5Hz), 2.36(3H, s), 2.54 (2H, q, J=7.5Hz), 3.14(4H, t), 3.45(4H, t), 3.95(3H, s), 6.83(1H, s), 6.92(2H, m), 7.03(5H, m), 7.15(1H, m), 7.31(2H m), 8.16(1H, s).	167-168°C
10		1.17(3H, t, J=7.5Hz), 2.38(3H, s), 2.55 (2H, q, J=7.5Hz), 3.27(4H, t, J=5.0Hz), 3.70(4H, t), 3.99(3H, s), 6.55(1H, d), 6.67(1H, s), 6.91(1H, m), 7.02(2H, d), 7.11(1H, m), 7.24(2H, m), 7.34(2H, m), 8.19(1H, s).	oil phase
11		1.19(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.14(4H, t), 3.68(4H, t), 3.97(3H, s), 6.92(1H, s), 6.94 (2H, m), 7.06(2H, m), 8.20(1H, s).	120-121°C
12		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.16(4H, t, J=5.0Hz), 3.66(4H, t, J=5.1Hz), 3.98(3H, s), 6.89 (1H, s), 6.91(2H, m), 6.99(2H, m), 8.19 (1H, s).	oil phase
13	$C_{20}H_{24}N_2O_2F_2$: theoretical, C, 61.53, H, 6.20, N, 14.35 experimental, C, 61.31, H, 6.27, N, 14.04	1.17(3H, t, J=7.5Hz), 2.38(3H, s), 2.56 (2H, q), 3.29(4H, t, J=5.5Hz), 3.68(4H, t, J=5.5Hz), 3.99(3H, s), 6.28(1H, m), 6.32(2H, d), 6.89(1H, s), 8.18(1H, s).	115-116°C
14		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.56 (2H, q, J=7.5Hz), 3.31(4H, t, J=5.0Hz), 3.69(4H, t, J=5.0Hz), 3.98(3H, s), 6.91(1H, d), 7.09(1H, d), 7.12(2H, m), 7.39(1H, m), 8.19(1H, s).	113-115°C
15		1.19(3H, t, J=7.5Hz), 2.38(3H, s), 2.56 (2H, q, J=7.0Hz), 3.10(4H, t, J=5.0Hz), 3.69(4H, t, J=5.0Hz), 3.99(3H, s), 6.82(1H, d), 6.91(1H, s), 7.04(2H, m), 7.40(1H, m), 8.22(1H, s).	97-99°C
16	$C_{20}H_{22}N_4O_2Cl_1$: theoretical, C, 61.77, H, 6.48, N, 14.41 experimental, C, 61.79, H, 6.54, N, 14.26	1.17(3H, t, J=7.5Hz), 2.38(3H, s), 2.55 (2H, q, J=7.5Hz), 3.26(4H, t, J=5.0Hz), 3.66(4H, t, J=5.0Hz), 3.98(3H, s), 6.79 (1H, d), 6.86(1H, d), 6.89(2H, d), 7.19 (1H, m), 8.18(1H, m).	104-105°C

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
17		1.17(3H, t, J=7.5Hz), 2.38(3H, s), 2.51 (2H, q, J=5.0Hz), 3.48(4H, t, J=5.0Hz), 3.75(4H, t, J=5.0Hz), 3.98(3H, s), 6.84 (3H, m), 8.35(1H, s).	74-75°C
18		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.54 (2H, q, J=7.5Hz), 3.26(4H, t, J=5.0Hz), 3.77(4H, t, J=5.0Hz), 3.98(3H, s), 6.85 (1H, s), 6.97(2H, m), 7.31(1H, m), 8.19(1H, s).	85-86°C
19		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.26(4H, t), 3.69(4H, t), 3.98(3H, s), 6.84(1H, m), 6.91 (1H, s), 6.96(2h, m), 7.29(1H, m), 8.19 (1H, s).	oil phase
20		1.18(3H, t, J=7.5Hz), 2.39(3H, s), 2.56 (2H, q, J=7.0Hz), 3.28(4H, t, J=4.5Hz), 3.65(4H, t, J=4.5Hz), 3.99(3H, s), 6.90 (1H, s), 7.26(2H, m), 8.23(1H, s).	162-163°C
21		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.27(4H, t), 3.69(4H, t), 3.98(3H, s), 6.84(1H, s), 6.98(3H, m), 7.39(1H, m), 8.35(1H, s).	94-94°C
22		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.56 (2H, q, J=7.5Hz), 3.27(4H, t), 3.74(4H, t), 3.98(3H, s), 6.91(1H, s), 6.98(3H, m), 7.46(1H, m), 8.19(1H, s).	99-101°C
23		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.25(4H, t, J=5.0Hz), 3.67(4H, t, J=5.0Hz), 3.98(3H, s), 6.94 (2H, m), 7.29(2H, m), 8.21(1H, s).	97-98°C
24		1.17(3H, t, J=7.5Hz), 2.38(3H, s), 2.55 (2H, q, J=7.5Hz), 3.48(4H, t, J=5.0Hz), 3.75(4H, t, J=5.0Hz), 3.96(3H, s), 6.84 (2H, m), 7.22(1H, s), 8.18(1H, s).	oil phase

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
25		1.17(3H, t, J=7.5Hz), 2.38(3H, s), 2.55 (2H, q, J=7.5Hz), 3.48(4H, t, J=5.0Hz), 3.75(4H, t, J=4.5Hz), 3.96(3H, s), 6.81 (1H, s), 6.84(2H, m), 7.22(1H, s), 8.18(1H, s).	oil phase
26		1.18(3H, t, J=7.5Hz), 2.34(3H, s), 2.37 (3H, s), 2.57(2H, q, J=7.5Hz), 2.96(4H, t, J=5.0Hz), 3.65(4H, t, J=4.5Hz), 3.97 (3H, s), 6.92(1H, s), 7.02(2H, m), 7.17 (2H, m), 8.21(1H, s).	129-130℃
27		1.17(3H, t, J=7.5Hz), 2.28(3H, s), 2.37 (3H, s), 2.55(2H, q, J=7.5Hz), 3.18(4H, t, J=5.0Hz), 3.66(4H, t, J=5.0Hz), 3.97 (3H, s), 6.87(2H, m), 6.91(1H, s), 7.11 (2H, m), 8.19(1H, s).	oil phase
28	$C_{22}H_{30}N_4O_2$: theoretical, C, 69.08, H, 7.91, N, 14.65 experimental, C, 68.48, H, 8.04, N, 14.04	1.18(3H, t, J=7.5Hz), 2.25(3H, s), 2.28 (3H, s), 2.37(3H, s), 2.56(2H, q, J=7.5 Hz), 2.95(4H, t), 3.65(4H, t), 3.97(3H , s), 6.89(2H, m), 7.07(1H, m), 8.21 (1H, s).	99-100℃
29	$C_{22}H_{30}N_4O_2$: theoretical, C, 69.08, H, 7.91, N, 14.65 experimental, C, 69.31, H, 7.82, N, 14.14	1.17(3H, t, J=7.5Hz), 2.29(6H, s), 2.44 (3H, s), 2.55(2H, q), 3.22(4H, t, J=4.5 Hz), 3.73(4H, t, J=4.5Hz), 3.98(3H, s), 6.42 (3H, s), 6.90(1H, s), 8.35(1H, s).	83-84℃
30		1.18(3H, t, J=8.0Hz), 2.33(6H, s), 2.39 (3H, s), 2.53(2H, q, J=7.5Hz), 3.15(4H, t, J=5.0Hz), 3.60(4H, t, J=5.0Hz), 4.00 (3H, s), 6.91(1H, s), 6.99(3H, m), 8.24(1H, s).	122-123℃
31		1.17(3H, t, J=7.5Hz), 1.22(3H, s), 1.23 (3H, s), 2.37(3H, s), 2.55(2H, q, J=7.5 Hz), 2.87(1H, m), 3.21(4H, t), 3.67 (4H, t), 3.97(3H, s), 6.90(3H, m), 7.17 (2H, d), 8.35(1H, s).	99-100℃
32		1.15(3H, t, J=7.5Hz), 1.22(3H, s), 1.23 (3H, s), 2.38(3H, s), 2.94(4H, t), 3.07 (1H, m), 3.16(4H, t), 4.00(3H, s), 6.84 (1H, s), 7.16(3H, m), 7.30(1H, m), 8.22(1H, s).	137-139℃

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
33		0.91(3H, t, J=7.5Hz), 1.17(3H, t, J=7.5Hz), 1.35(2H, m), 1.59(2H, m), 2.37(3H, s), 2.55(4H, q, J=4.0Hz), 3.20 (4H, t, J=5.0Hz), 3.66(4H, t, J=5.0Hz), 3.97(3H, s), 6.82(2H, m), 6.88(1H, s), 7.11(2H, m), 8.19(1H, s).	72-73°C
34		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.56(3H, s), 2.57(2H, q, J=7.5Hz), 3.55(4H, t), 3.69(4H, t), 3.98(3H, s), 6.88(3H, m), 7.91(2H, m), 8.18(1H. s).	149-150°C
35		1.15(3H, t, J=7.5Hz), 2.37(3H, s), 2.54 (2H, q, J=7.5Hz), 2.89(4H, t, J=4.8Hz), 3.38(4H, t, J=4.8Hz), 3.95(3H, s), 6.78 (1H, s), 7.03(1H, d), 7.12(1H, m), 7.31 (3H, m), 7.41(2H, m), 7.63(2H, m), 8.17(1H, s).	oil phase
36		1.18(3H, t, J=7.5Hz), 2.38(3H, s), 2.56 (2H, q, J=7.5Hz), 3.32(4H, t), 3.72(4H, t), 3.99(3H, s), 6.92(1H, s), 7.04(2H, m), 7.40(2H, m), 7.57(5H, m), 8.20(1H, s).	160-161°C
37		1.18(3H, t, J=7.5Hz), 2.38(3H, s), 2.97 (4H, t), 3.70(4H, t), 3.98(1H, s), 6.92 (2H, m), 7.11(2H, m), 8.19(1H, s).	oil phase
38	$C_{20}H_{26}N_4O_3$: theoretical, C, 64.85, H, 7.07, N, 15.12 experimental, C, 59.89, H, 7.17, N, 14.73	1.16(3H, t, J=7.5Hz), 2.39(3H, s), 3.23 (4H, t, J=5.0Hz), 3.67(4H, t), 3.98(3H, s), 6.39(1H, d), 6.45(1H, s), 6.51(1H, d), 6.90(1H, s), 7.13(1H, m), 8.17(1H, s).	148-149°C
39		1.18(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.16(4H, t), 3.73(4H, t), 3.98(3H, s), 6.80(2H, m), 6.91(2H, m), 8.17(1H, s)	103-104°C
40		1.17(3H, t, J=7.5Hz), 2.29(3H, s), 2.38 (3H, s), 2.56(2H, q, J=7.5Hz), 3.24(4H, t), 3.72(4H, t), 3.99(3H, s), 6.90(1H, s), 7.03(4H, m), 8.21(1H, s).	161-162°C

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
41	$C_{22}H_{28}N_4O_4$: theoretical, C, 64.06, H, 6.84, N, 13.58 experimental, C, 64.31, H, 13.50, N, 7.00	1.17(3H, t, J=7.5Hz), 2.29(3H, s), 2.38 (3H, t), 2.56(2H, q, J=7.5Hz), 3.28(4H, t, J=5.0Hz), 3.68(4H, t), 3.99(3H, s), 6.65 (2H, m), 6.84(1H, d). 6.89(1H, s), 7.30 (1H, m), 8.19(1H, s).	90-91°C
42		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.18(4H, t), 3.68(4H, t), 3.99(3H, s), 6.89(2H, m), 6.99(2H, m), 8.19(1H, s).	oil phase
43		1.18(3H, t, J=7.5Hz), 2.37(3H, s), 2.54 (2H, q, J=7.5Hz), 2.89(3H, s), 2.97(4H, t), 3.65(4H, t), 3.96(3H, s), 6.77(2H, m), 6.94(1H, s), 7.03(1H, d), 7.13(1H, m).	108-109°C
44		1.17(3H, t, J=7.5Hz), 2.26(3H, s), 2.57 (2H, q), 3.17(4H, t), 3.79(1H, d), 4.00 (3H, s), 6.91 (1H, s), 7.09(1H, d), 7.42 (1H, m), 7.50(3H, m), 7.59(1H, d), 7.84 (1H, d).	159-160°C
45		1.17(3H, t, J=7.5Hz), 2.47(3H, s), 2.56 (2H, q), 3.04(4H, t), 4.05(3H, s), 6.97 (1H, s), 7.49(4H, m), 8.01(2H, m), 8.27 (2H, m), 8.43(1H, s).	oil phase
46		1.18(3H, t, J=7.5Hz), 2.26(3H, s), 2.39 (3H, s), 2.56(2H, q, J=7.5Hz), 2.82(2H, m), 3.20(2H, m), 3.46(2H, m), 3.78(3H, s), 3.99(2H, m), 4.14(3H, s), 6.71(1H, d), 6.82(1H, d), 6.91(1H, s), 7.04(1H, m), 8.25(1H, s).	151-152°C
47	$C_{22}H_{30}N_4O_3$: theoretical, C, 66.31, H, 7.59, N, 14.06 experimental, C, 66.46, H, 7.75, N, 13.71	1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.49 (3H, s), 2.55(2H, q, J=7.5Hz), 3.11(4H, t), 3.77(4H, t), 3.86(3H, s), 3.96(3H, s), 6.77(3H, m), 8.37(1H, s).	90-91°C
48	$C_{22}H_{30}N_4O_3$: theoretical, C, 66.31, H, 7.59, N, 14.06 experimental, C, 65.24, H, 7.49, N, 13.91	1.17(3H, t, J=7.5Hz), 2.23(3H, s), 2.37 (3H, s), 2.38(3H, s), 2.53(2H, q, J=7.5Hz), 2.95(4H, t, J=4.8Hz), 3.65(4H, t, J=4.6Hz), 3.96(3H, s), 3.98(3H, s), 6.57(2H, m), 6.84(1H, s), 7.03(1H, s), 8.20(1H, s).	84-85°C

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
49		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.12(4H, t), 3.70(4H, t), 3.89(3H, s), 3.97(3H, s), 6.80(2H, m), 6.94(1H, s), 8.21(1H, s).	97-98℃
50		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.57 (2H, q, J=7.5Hz), 3.27(4H, t), 3.69(4H, t), 3.80(3H, s), 3.98(3H, s), 6.50(1H, m), 6.90(1H, s), 7.54(1H, m), 7.71(1H, m), 8.19(1H s).	oil phase
51		1.19(3H, t, J=7.5Hz), 2.37(3H, s), 2.55(2H, q, J=7.5Hz), 3.13(4H, t), 3.67 (4H, t), 3.78(3H, s), 3.97(3H, s), 6.87 (3H, m), 8.19(1H, s).	94-95℃
52		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.15(4H, t), 3.69(4H, t), 3.83(3H, s), 3.98(3H, s), 6.46(1H, d), 6.69(1H, d), 6.90(1H, s), 8.18(1H, s).	149-150℃
53		1.17(3H, t, J=7.5Hz), 2.31(3H, s), 2.37 (3H, s), 2.55(2H, q, J=7.5Hz), 3.14(4H, t), 3.66(4H, t), 3.79(3H, s), 3.95(3H, s), 6.77(1H, s), 6.92(2H, m), 8.18(1H, s).	128-129℃
54		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.56 (2H, q, J=7.5Hz), 3.19(4H, t), 3.73(4H, t), 3.93(3H, s), 3.98(3H, s), 6.82(1H, s), 6.84(2H, m), 7.31(2H, m), 7.42(2H, m), 7.53(2H, m), 8.21(1H, s).	134-135℃
55	$C_{21}H_{27}N_4O_3Cl_1$: theoretical, C, 60.20, H, 6.50, N, 13.37 experimental, C, 59.33, H, 6.16, N, 12.80	1.17(3H, t, J=7.5Hz), 2.23(3H, s), 2.38 (3H, s), 2.56(2H, q, J=7.5Hz), 2.95(4H, t, J=5.0Hz), 3.66(4H, t), 3.99(3H, s), 6.58(1H, d), 6.64(1H, d), 6.91(1H, s), 7.05(1H, m), 8.21(1H, s).	188-189℃
56	$C_{21}H_{28}N_4O_3$: theoretical, C, 65.60, H, 7.34, N, 14.57 experimental, C, 65.65, H, 7.32, N, 14.40	1.18(3H, t, J=8.0Hz), 2.36(3H, s), 2.41 (3H, s), 2.57(2H, q, J=7.5Hz), 2.93(2H, m), 3.20(2H, m), 3.43(2H, m), 3.99(3H, s), 4.11(2H, m), 6.60(1H, d), 6.83(2H, d), 6.93(1H, s), 7.15(1H, m), 8.23(1H, s).	208-211℃

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
57		1.18(3H, t, J=7.5Hz), 2.29(3H, s), 2.38 (3H, s), 2.56(2H, q, J=7.5Hz), 2.97(4H, t), 3.71(4H, t), 3.98(3H, s), 6.69(1H, d), 6.82(1H, s), 6.90(1H, s), 7.05(1H, d), 8.18(1H, s).	192-193°C
58		1.13(3H, t, J=7.5Hz), 2.24(3H, s), 2.55 (2H, q, J=7.5Hz), 3.48(4H, t, J=5.0Hz), 3.75(4H, t, J=5.0Hz), 3.97(3H, s), 6.89 (2H, m), 7.20(1H, s), 8.35(1H, s).	74-75°C
59		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.04(4H, t, J=5.0Hz), 3.68(4H, t, J=5.0Hz), 3.98(3H, s), 6.94(2H, m), 6.98(1H, m), 8.19(1H, s).	85-86°C
60	$C_{22}H_{30}N_4O_3$: theoretical, C, 66.31, H, 7.59, N, 14.06 experimental, C, 65.38, H, 7.65, N, 13.74	1.11(3H, t, J=7.5Hz), 2.38(3H, s), 2.54 (2H, q, J=7.5Hz), 3.05(4H, t, J=5.0Hz), 3.53(4H, t, J=4.5Hz), 3.86(3H, s), 3.95 (3H, s), 4.33(2H, d), 6.86(1H, d), 6.93 (2H, m), 7.01(1H, m), 7.25(1H, s).	oil phase
61	$C_{21}H_{27}N_4O_2F_1$: theoretical, C, 65.27, H, 7.04, N, 14.50 experimental, C, 65.87, H, 7.35, N, 14.48	1.14(3H, t, J=7.5Hz), 2.40(3H, s), 2.54 (2H, q, J=7.5Hz), 3.04(4H, t, J=5.0Hz), 3.52(4H, t, J=5.0Hz), 3.96(3H, s), 4.33(2H, d), 6.92(2H, m), 7.06(2H, m), 7.32(1H, s).	oil phase
62		1.16(3H, t, J=7.5Hz), 2.40(3H, s), 2.54 (2H, q, J=7.5Hz), 3.07(4H, t, J=5.0Hz), 3.50(4H, t, J=5.0Hz), 3.95(3H, s), 4.34 (2H, d), 6.85(2H, m), 6.97(2H, m), 7.32(1H, s).	oil phase
63		1.15(3H, t, J=8.0Hz), 2.38(3H, s), 2.54 (2H, q, J=7.5Hz), 3.16(4H, t, J=5.0Hz), 3.49(4H, t, J=5.0Hz), 3.96(3H, s), 4.33 (2H, d), 6.75(1H, m), 6.85(2H, m), 7.15 (1H, m), 7.46(2H, s).	oil phase
64		1.15(3H, t, J=7.5Hz), 2.40(3H, s), 2.53 (2H, q, J=7.5Hz), 2.76(2H, t, J=6.5Hz), 3.05(4H, t, J=4.8Hz), 3.47(6H, m), 3.93 (3H, s), 6.87(2H, m), 6.97(2H, m), 7.26(1H, s).	oil phase

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
65		1.14(3H,t,J=7.5Hz), 2.43(3H,s), 2.51 (2H,q,J=7.5Hz), 2.76(2H,m), 3.00(4H, t,J=5.0Hz), 3.44(2H,m), 3.50(4H,t), 3.87(3H,s), 3.93(3H,s), 6.72(1H,m), 6.92(2H,m), 7.01(1H,m), 7.16(1H,s).	oil phase
66		1.16(3H,t,J=7.5Hz), 1.80(2H,q), 2.40 (3H,s), 2.53(2H,q), 2.58(2H,t), 3.26 (2H,q), 3.89(3H,s), 3.93(3H,s), 6.92 (4H,m), 7.16(1H,s).	oil phase
67		1.15(3H,t,J=7.5Hz), 1.38(2H,m), 1.58 (4H,m), 2.39(3H,s), 2.52(4H,m), 3.06 (4H,t), 3.25(2H,m), 3.55(4H,t), 3.87 (3H,s), 3.91(3H,s), 6.88(2H,m), 6.94 (2H,m), 7.46(1H,s).	128-129℃
68		1.15(3H,t,J=7.5Hz), 1.33(6H,m), 1.52 (2H,m), 2.39(3H,s), 2.52(4H,m), 3.05 (4H,t), 3.25(2H,m), 3.54(4H,t), 3.87 (3H,s), 3.90(3H,s), 6.87(2H,m), 6.93 (2H,m), 7.10(1H,s).	118-120℃
69		1.20(3H,t), 2.39(3H,s), 2.58(2H,q), 2.83(4H,t), 3.20(6H,brs), 3.90(3H,s), 3.98(3H,s), 7.00(4H,m), 8.40(1H,s).	164-165℃
70		1.18(3H,t), 2.39(3H,s), 2.56(2H,q), 2.77(4H,t), 3.21(2H,m), 3.28(4H,t), 6.82(2H,m), 6.90(1H,s), 7.19(1H,m), 8.37(1H,s).	120-123℃
71		1.18(3H,t), 2.39(3H,s), 2.56(2H,q), 2.81(4H,t), 3.20(6H,brs), 3.97(3H,s), 7.04(4H,m), 8.38(1H,s).	139-140℃
72		1.16(3H,t,J=7.5Hz), 2.36(3H,s), 2.54 (6H,m), 3.96(3H,s), 6.85(1H,s), 7.33(5H,s).	96-97℃

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
73		1.16(3H, t, J=7.5Hz), 2.36(3H, s), 2.52 (6H, m), 3.53(6H, m), 3.81(3H, s), 3.95 (3H, s), 6.84(1H, s), 6.88(2H, m), 7.27 (2H, m), 8.16(1H, s).	96-98°C
74		1.17(3H, t, J=7.5Hz), 2.37(3H, s), 2.52 (2H, q), 2.65(4H, t), 3.61(6H, m), 3.83 (3H, s), 3.95(3H, s), 6.83(1H, s), 6.90 (2H, m), 6.97(2H, m), 8.15(1H, s).	83-84°C
75		1.16(3H, t, J=7.5Hz), 2.37(3H, s), 2.54 (6H, m), 3.53(6H, m), 3.97(3H, s), 6.85 (1H, s), 7.02(2H, m), 7.32(2H, m), 8.17(1H, s).	74-75°C
76		1.17(3H, t, J=7.5Hz), 1.39(3H, t, J= 7.0Hz), 2.35(3H, s), 2.55(2H, q, J= 5.0Hz), 3.13(4H, t, J=4.6Hz), 3.68(4H, t, J=4.6Hz), 3.89(3H, s), 4.42(2H, q, J= 9.3Hz), 6.90(1H, d), 6.96(2H, m), 7.04 (1H, m), 8.21(1H, s).	114-115°C
77		1.17(3H, t, J=7.5Hz), 1.40(3H, t, J= 7.0Hz), 2.38(3H, s), 2.55(2H, q, J= 7.5Hz), 3.14(4H, t, J=4.5Hz), 3.68 (4H, t, J=4.5Hz), 4.43(2H, q, J=7.0Hz), 6.96(2H, m), 7.08(2H, m), 8.19(1H, s).	126-127°C
78		1.17(3H, t, J=7.5Hz), 1.40(3H, t, J= 7.5Hz), 2.35(3H, s), 2.55(2H, q, J=7.5 Hz), 3.27(4H, t, J=5.0Hz), 3.66(4H, t, J=5.0Hz), 4.43(2H, q, J=7.0Hz), 6.79 (1H, d), 6.81(1H, d), 6.86(1H, s), 6.94 (1H, s), 7.19(1H, m), 8.18(1H, s).	101-102°C
79		1.17(3H, t, J=7.5Hz), 1.40(3H, t, J= 7.0Hz), 1.49(3H, t, J=6.9Hz), 2.35(3H, s), 2.55(2H, q), 3.14(4H, t), 3.68(4H, t), 4.10(2H, q), 4.44(2H, q), 6.87(1H, d), 6.92(2H, m), 6.96(1H, s), 7.00(1H, m), 8.20(1H, s).	oil phase
80		1.22(3H, t, J=7.5Hz), 2.31(3H, s), 2.58 (2H, q, J=7.5Hz), 3.08(4H, t), 3.66(4H, t), 3.88(3H, s), 6.96(3H, m), 7.13(2H, m), 7.23(2H, m), 7.36(2H, m), 8.36(1H, s).	104-105°C

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
81		1.22(3H, t, J=7.5Hz), 2.31(3H, s), 2.60 (2H, q, J=7.5Hz), 3.22(4H, t), 3.66(4H, t), 3.88(3H, s), 6.93(1H, s), 6.96(3H, m), 7.13(2H, m), 7.23(2H, m), 7.36(2H, m), 8.36(1H, s).	120-121°C
82		1.22(3H, t, J=7.5Hz), 2.29(3H, s), 2.34 (3H, s), 2.60(2H, q, J=7.5Hz), 3.24(4H, t, J=5.0Hz), 3.63(4H, t, J=4.5Hz), 6.62 (2H, m), 6.80(1H, d), 6.93(1H, s), 7.10 (2H, m), 7.17(1H, m), 7.27(1H, m), 7.46 (2H, m), 8.34(1H, s).	52-53°C
83		1.22(3H, t, J=7.5Hz), 2.31(3H, s), 2.60 (2H, q), 3.11(4H, t, J=4.8Hz), 3.65(4H, t, J=4.8Hz), 6.99(3H, m), 7.09(4H, m), 7.36(2H, m), 8.35(1H, s).	166-167°C
84		1.23(3H, t, J=7.5Hz), 2.28(3H, s), 2.31 (3H, s), 2.60(2H, q, J=7.5Hz), 3.19(4H, t, J=5.0Hz), 3.95(4H, t), 6.55(3H, m), 6.94(1H, s), 7.09(2H, m), 7.20(1H, m), 7.38(2H, m), 8.35(1H, s).	oil phase
85		1.25(3H, t, J=7.2Hz), 2.30(3H, s), 2.60 (2H, q, J=7.5Hz), 3.21(4H, t, J=5.2Hz), 3.62(4H, t), 3.77(6H, s), 6.08(3H, m), 7.13(2H, m), 6.93(1H, s), 7.16(1H, m), 7.36(2H, m), 8.34(1H, s).	94-95°C
86		1.19(3H, t, J=7.5Hz), 2.37(3H, s), 2.55 (2H, q, J=7.5Hz), 3.26(4H, t, J=5.0Hz), 3.78(4H, t, J=6.0Hz), 3.98(3H, s), 6.91 (1H, s), 6.97(2H, m), 7.31(1H, m), 8.91(1H, s).	156-157°C
87		1.22(3H, t, J=8.0Hz), 2.31(3H, s), 2.60 (2H, q, J=7.5Hz), 3.10(4H, t), 3.66(4H, t), 3.99(3H, s), 6.79(1H, m), 6.91(1H, s), 6.93(2H, m), 7.10(2H, m), 7.16(1H, m), 7.38(2H, m), 8.34(1H, s).	117-118°C
88		1.23(3H, t, J=7.5Hz), 2.18(3H, s), 2.60 (2H, q, J=7.5Hz), 3.22(4H, t, J=4.5Hz), 3.95(4H, t), 6.40(1H, m), 6.52(2H, m), 7.13(2H, m), 7.37(2H, m), 8.32(1H, s).	92-93°C

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
89		1.24(3H, t, J=7.5Hz), 2.52(3H, s), 2.66 (2H, q, J=8.0Hz), 3.21(4H, t), 3.45(3H, s), 3.82(4H, t), 4.12(3H, s), 7.02(4H, m), 7.43(1H, s).	185-186°C
90		1.25(3H, t, J=7.5Hz), 2.52(3H, s), 2.65 (2H, q), 3.45(3H, s), 3.89(6H, s), 6.95 (3H, m), 7.43(1H, s).	102-103°C
91		1.22(3H, t, J=7.5Hz), 2.53(3H, s), 2.66 (2H, q, J=7.5Hz), 3.35(4H, t), 3.47(3H, s), 3.81(4H, t), 4.23(1H, q, J=5.7Hz), 6.88(2H, m), 6.94(1H, s), 7.22(2H, m), 7.71(1H, s).	oil phase
92		1.22(3H, t, J=7.5Hz), 2.49(3H, s), 2.63 (2H, q, J=8.0Hz), 3.11(4H, t, J=5.0Hz), 3.70(4H, t, J=5.0Hz), 3.72(6H, s), 6.68 (1H, m), 6.88(2H, m), 7.05(1H, m), 7.88 (1H, s), 8.23(1H, s).	161-162°C
93		1.21(3H, t, J=7.5HZ), 2.42(3H, s), 2.63 (2H, q, J=7.5Hz), 3.24(4H, t, J=5.0Hz), 3.67(4H, t, J=5.0Hz), 3.78(6H, s), 6.05 (1H, s), 6.09(2H, s), 7.89(1H, s), 8.26(1H, s).	179-180°C
94		1.20(3H, t, J=7.5Hz), 2.40(3H, s), 2.57 (2H, q, J=7.5Hz), 3.02(4H, t), 3.09(4H, t), 3.28(4H, t), 3.68(4H, t), 6.80(2H, d), 6.82(1H, d), 6.90(1H, s), 7.22(1H, m), 8.22(1H, s).	oil phase
95		1.20(3H, t, J=7.5Hz), 1.48(9H, s), 2.39 (3H, s), 2.58(2H, q), 2.95(4H, t), 3.28 (4H, t), 3.57(4H, t), 3.67(4H, t), 6.79 (1H, dd), 6.87(1H, dd), 7.21(1H, m), 7.26(1H, s), 8.24(1H, s).	188-189°C
96		1.20(3H, t, J=7.5Hz), 1.48(9H, s), 2.39 (3H, s), 2.58(2H, q), 2.95(4H, t), 3.12 (4H, t), 3.57(4H, t), 3.70(4H, t), 3.91 (3H, s), 6.94(3H, m), 7.06(1H, m), 7.58(1H, s), 8.25(1H, s).	152-153°C

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
97	$C_{21}H_{28}N_4O_2S_1$: theoretical, C, 62.97, H, 7.05, N, 13.99, S, 8.00 experimental, C, 62.61, H, 6.96, N, 14.08, S, 7.77	1.19(3H, t, J=7.5Hz), 2.39(3H, s), 2.57 (2H, q, J=7.5Hz), 3.16(4H, t, J=5.0Hz), 3.89(3H, s), 3.96(3H, s), 4.10(4H, t, J=4.5Hz), 6.89(1H, m), 6.93(2H, m), 7.04 (1H, m), 8.11(1H, s).	133-134°C
98		1.17(3H, t), 2.47(3H, s), 2.55(2H, q, J=7.5Hz), 3.39(4H, t, J=5.1Hz), 3.98(3H, s), 4.18(4H, t), 6.79(1H, m), 6.90(2H, m), 7.19(1H, m), 8.11(1H, s).	90-91°C
99		1.19(3H, t, J=7.5Hz), 2.39(3H, s), 2.58 (2H, q, J=7.5Hz), 3.19(4H, t, J=5.0Hz), 3.96(3H, s), 4.09(4H, t, J=5.0Hz), 6.95 (2H, m), 7.00(2H, m), 8.11(1H, s).	132-133°C
100	$C_{22}H_{30}N_4O_3S_1$: theoretical, C, 61.37, H, 7.02, N, 13.01, S, 7.45 experimental, C, 61.47, H, 7.25, N, 13.21, S, 7.47	1.19(3H, t, J=7.5Hz), 2.40(3H, s), 2.58 (2H, q, J=7.5Hz), 3.36(4H, t, J=4.5Hz), 3.75(6H, s), 3.96(3H, s), 4.13(4H, t), 6.09(3H, m), 8.13(1H, s).	166-167°C
101		1.20(3H, t, J=7.5Hz), 2.40(3H, s), 2.58 (2H, q, J=8.0Hz), 3.37(4H, t), 3.96(3H, s), 4.15(4H, t), 6.98(2H, m), 7.46(1H, s), 8.13(1H, s).	163-164°C
102		1.18(3H, t, J=8.0Hz), 2.40(3H, s), 2.55 (2H, q, J=7.5Hz), 3.11(4H, t), 3.75(2H, t), 3.87(2H, t), 3.89(3H, s), 3.97(3H, s), 6.86(1H, d), 6.94(2H, m), 7.04(1H, m), 7.26(1H, s).	89-90°C
103		1.26(3H, t, J=7.5Hz), 2.40(3H, s), 2.55 (2H, q), 3.25(4H, t), 3.72(2H, t), 3.84 (2H, t), 3.93(3H, s), 6.82(1H, d), 6.86 (1H, d), 6.92(1H, s), 7.04(1H, s), 7.22 (1H, m), 7.46(1H, s).	119-120°C
104		1.17(3H, t, J=7.5Hz), 2.39(3H, s), 2.53 (2H, q, J=7.5Hz), 3.23(4H, t, J=5.0Hz), 3.64(2H, t), 3.79(6H, s), 3.79(2H, t), 5.96(1H, s), 6.12(2H, s), 7.30(1H, s).	oil phase

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
105		1.17(3H, t, J=7.5Hz), 2.42(3H, s), 2.56 (2H, q, J=7.5Hz), 3.01(4H, t), 3.78(4H, t), 3.87(3H, s), 3.93(3H, s), 5.11(2H, s), 6.91(3H, m), 7.03(1H, m), 7.33(1H, s).	oil phase
106		1.15(3H, t, J=7.5Hz), 2.42(3H, s), 2.54 (2H, q), 3.15(4H, t), 3.64(4H, t), 3.93 (3H, s), 3.96(3H, s), 4.59(2H, s), 6.85 (3H, m), 7.15(1H, s), 7.33(1H, s).	oil phase
107		2.19(3H, s), 2.34(3H, s), 3.26(4H, t), 3.69(4H, t), 3.97(3H, s), 6.82(1H, s), 6.94(3H, m), 7.30(2H, m), 8.14(1H, s).	140-141°C
108	$C_{20}H_{26}N_4O_3$: theoretical, C, 64.85, H, 7.07, N, 15.12 experimental, C, 65.13, H, 7.24, N, 15.10	1.55(3H, s), 2.19(3H, s), 2,33(3H, s), 3.12(4H, t), 3.69(4H, t), 3.89(3H, s), 3.97(3H, s), 6.89(2H, m), 6.90(1H, s), 7.04(2H, m), 8.16(1H, s).	135-136°C
109	$C_{19}H_{23}N_4O_2Cl_1$: theoretical, C, 60.88, H, 6.18, N, 14.95 experimental, C, 60.87, H, 6.28, N, 14.86	2.19(3H, s), 2.34(3H, s), 3.27(4H, t, J= 5.2Hz), 3.66(4H, t, J=5.0Hz), 3.98 (3H, s), 6.80(1H, d), 6.86(2H, m), 6.90 (1H, s), 7.21(1H, m), 8.14(1H, s).	95-96°C
110		2.19(3H, s), 2.34(3H, s), 3.14(4H, t, J= 4.9Hz), 3.68(4H, t, J=4.8Hz), 3.98(3H, s), 6.88(1H, s), 6.98(2H, m), 7.09(2H, m), 8.15(1H, s).	164-167°C
111		2.20(3H, s), 2.39(3H, s), 3.29(4H, t, J= 5.0Hz), 3.67(4H, t, J=5.0Hz), 4.04(3H, s), 6.30(1H, m), 6.38(2H, d), 6.86(1H, s), 8.18(1H, s).	133-134°C
112		2.19(3H, s), 2.35(3H, s), 2.99(4H, t), 3.72(4H, t), 3.98(3H, s), 6.90(2H, m), 7.15(2H, m), 8.14(1H, s).	174-175°C

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
113		2.18(3H, s), 2.33(3H, s), 3.25(4H, t, J= 5.0Hz), 3.67(4H, t, J=4.3Hz), 3.97(3H, s), 6.38(1H, d), 6.46(1H, s), 6.54(1H, d), 6.87(1H, s), 7.13(1H, t), 8.13(1H, s).	176-178℃
114		2.18(3H, s), 2.33(3H, s), 3.12(4H, t), 3.68(4H, t), 3.97(3H, s), 6.80(2H, m), 6.91(2H, m), 8.13(1H, s).	168-169℃
115		2.09(3H, s), 2.29(3H, s), 2.34(3H, s), 3.27(4H, t, J=5.0Hz), 3.67(4H, t, J=5.0Hz), 3.98(3H, s), 6.44(2H, m), 6.81(1H, m), 6.88(1H, s), 8.14(1H, s).	108-109℃
116		2.19(3H, s), 2.28(3H, s), 2.34(3H, s), 3.22(4H, t), 3.68(4H, t), 3.98(3H, s), 6.87(1H, s), 7.01(4H, m), 8.14(1H, s).	159-160℃
117		2.04(3H, s), 2.31(3H, s), 2.34(3H, s), 3.20(4H, t), 3.76(4H, t), 3.81(3H, s), 3.98(3H, s), 6.86(1H, s), 7.01(3H, m), 8.15(1H, s).	139-140℃
118	$C_{21}H_{28}N_4O_4$: theoretical, C, 62.98, H, 7.05, N, 13.99 experimental, C, 63.21, H, 7.19, N, 13.96	2.18(3H, s), 2.33(3H, s), 3.25(4H, t, J= 5.0Hz), 3.67(4H, t), 3.80(6H, s), 3.97 (3H, s), 6.07(3H, m), 6.86(1H, s), 8.14 (1H, s).	150-151℃
119	$C_{21}H_{30}N_4O_2$: theoretical, C, 68.45, H, 7.66, N, 15.20 experimental, C, 68.26, H, 7.97, N, 14.99	2.19(3H, s), 2.26(3H, s), 2.28(3H, s), 2.34(3H, s), 2.94(4H, t), 3.66(4H, t), 3.97(3H, s), 6.89(3H, m), 8.33(1H, s).	134-135℃
120		2.16(3H, s), 2.29(6H, s), 2.33(3H, s), 3.23(4H, t), 3.66(4H, t), 3.97(3H, s), 6.53(3H, m), 6.87(1H, s), 8.14(1H, s).	125-126℃

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
121		2.19(3H,s), 2.26(3H,s), 2.34(3H,s), 2.95(4H,t,J=4.8Hz), 3.64(4H,t,J=4.8Hz), 3.78(3H,s), 3.97(3H,s), 6.57(1H,d), 6.58(1H,s), 7.11(1H,d), 8.32(1H,s).	127-130℃
122		2.19(3H,s), 2.30(3H,s), 2.42(3H,s), 2.94(4H,t), 3.69(4H,t), 3.97(3H,s), 6.69(1H,d), 6.82(1H,s), 6.88(1H,s), 7.04(1H,d), 8.14(1H,s).	184-185℃
123		2.04(3H,s), 2.33(3H,s), 3.15(4H,t), 3.67(4H,t), 3.89(3H,s), 3.97(3H,s), 6.65(1H,d), 6.81(1H,d), 8.14(1H,s).	172-176℃
124		2.20(3H,s), 2.48(3H,s), 3.17(4H,t), 3.76(4H,t), 4.00(3H,s), 6.94(1H,s), 7.11(1H,d), 7.40(1H,m), 7.50(1H,m), 7.61(1H,d), 8.19(1H,s).	202-204℃
125		2.21(3H,s), 2.44(3H,s), 3.04(4H,t), 3.77(4H,t), 4.05(3H,s), 6.97(1H,m), 7.49(4H,m), 8.01(2H,m), 8.27(1H,m), 8.43(1H,s).	103-104℃
126		2.22(3H,s), 2.43(3H,s), 3.39(4H,t,J=5.0Hz), 4.02(3H,s), 4.17(4H,t), 6.87(1H,d), 6.91(1H,d), 6.96(1H,s), 7.24(2H,m), 8.12(1H,s).	168-169℃
127		2.21(3H,s), 2.42(3H,s), 3.38(4H,t,J=5.0Hz), 4.02(3H,s), 4.17(4H,t), 6.87(1H,s), 6.91(2H,d), 6.96(1H,s), 8.12(1H,s).	oil phase
128	$C_{20}H_{26}N_4O_2S_1$: theoretical. C,62.15,H,6.78,N,14.50,S,8.29 experimental. C,62.60,H,7.19,N,14.70,S,8.48	2.17(3H,s), 2.36(3H,s), 3.30(4H,t), 3.19(3H,s), 3.96(3H,s), 4.21(4H,t), 6.95(4H,m), 8.03(1H,s).	160-161℃

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
129		2.21(3H,s), 2.36(3H,s), 3.37(4H,t), 3.79(6H,s), 3.96(3H,s), 4.10(4H,t), 6.10(2H,m), 7.46(1H,s), 8.10(1H,s).	166-167℃
130		2.11(2H,m), 2.87(4H,m), 3.12(4H,t,J=4.95Hz), 3.70(4H,t,J=4.8Hz), 3.89(3H,s), 4.00(3H,s), 6.89(2H,m), 7.05(2H,m), 8.26(1H,s).	130-131℃
131		2.12(2H,m), 2.87(4H,m), 3.27(4H,t,J=5.0Hz), 3.67(4H,t,J=5.0Hz), 4.00(3H,s), 6.80(1H,m), 6.90(2H,m), 7.21(1H,m), 8.23(1H,s).	142-146℃
132		2.12(2H,m), 2.87(4H,m), 3.27(4H,t,J=5.0Hz), 3.68(4H,t,J=5.0Hz), 4.00(3H,s), 6.97(3H,m), 7.07(1H,m), 8.24(1H,s).	152-153℃
133		1.76(2H,m), 1.83(2H,m), 2.68(2H,t,J=5.7Hz), 2.72(2H,t,J=5.9Hz), 3.13(4H,t), 3.71(4H,t), 3.89(3H,s), 3.97(3H,s), 6.95(4H,m), 8.09(1H,s).	oil phase
134		1.75(2H,m), 1.83(2H,m), 2.68(2H,t,J=6.1Hz), 2.75(2H,t,J=6.0Hz), 3.27(4H,t,J=5.15Hz), 3.67(4H,t,J=4.9Hz), 4.00(3H,s), 6.81(1H,d), 6.90(2H,m), 7.20(1H,m), 8.08(1H,s).	oil phase
135		1.76(2H,m), 1.84(2H,m), 2.68(2H,t), 2.72(2H,t), 3.14(4H,t,J=5.0Hz), 3.68(4H,t,J=5.0Hz), 3.97(1H,s), 6.99(1H,s), 7.00(2H,m), 7.09(2H,m), 8.08(1H,s).	134-135℃
136		0.90(3H,s), 0.91(3H,s), 2.07(2H,m), 2.48(3H,d), 3.22(4H,t), 3.80(4H,t), 3.88(3H,s), 3.99(3H,s), 6.67(1H,d), 6.94(1H,s), 6.98(3H,m), 8.24(1H,s).	oil phase

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
137		0.90(3H,s), 0.91(3H,s), 2.07(1H,m), 2.49(3H,d), 3.29(3H,t,J=5.0Hz), 3.74 (4H,t,J=4.8Hz), 4.00(3H,s), 6.69(1H,m), 6.89(2H,m), 7.21(1H,m), 8.24(1H,m).	oil phase
138		0.91(3H,s), 0.92(3H,s), 2.08(1H,m), 2.54(3H,d), 3.32(4H,t), 3.95(4H,t), 4.20(3H,s), 6.70(1H,d), 6.93(1H,s), 7.14(3H,m), 8.26(1H,s).	oil phase
139		3.03(4H,t), 3.69(4H,t), 3.78(3H,s), 4.02(3H,s), 6.89(4H,m), 7.04(1H,s), 7.77(1H,dd), 8.40(1H,dd).	168-169°C
140		3.13(4H,t), 3.71(4H,t), 3.89(3H,s), 4.02(3H,s), 6.84(4H,m), 6.91(1H,m), 7.05(1H,m), 7.78(1H,m), 8.42(1H,m).	173-174°C
141		3.27(3H,t,J=5.0Hz), 3.69(4H,t), 4.03 (3H,s), 6.89(1H,m), 7.04(1H,s), 7.32 (2H,m), 7.78(1H,dd), 8.40(1H,dd).	133-135°C
142		3.28(4H,t,J=5.2Hz), 3.69(4H,t,J= 5.0Hz), 4.03(3H,s), 6.83(1H,m), 6.90 (3H,m), 7.20(1H,m), 7.79(1H,m), 8.40(1H,m).	95-96°C
143		1.17(3H,t,J=7.5Hz), 2.37(3H,s), 2.54 (2H,q), 3.17(4H,t,J=3.2Hz), 3.66(4H, t), 3.98(3H,s), 4.56(1H,s), 6.93(1H, s), 7.00(2H,m), 8.19(1H,s).	225-227°C
144		1.16(3H,t,J=7.5Hz), 2.40(3H,s), 2.54 (2H,q,J=7.5Hz), 3.07(4H,t), 3.49(4H,t), 3.95(3H,s), 4.34(2H,d), 4.53(1H,s), 6.97(2H,m), 7.32(1H,s), 7.79(1H,s).	143-145°C

example number	elementary analysis	^{1}H NMR (500MHz, $CDCl_3$) δ	melting point
145		1.11(3H, t, J=7.5Hz), 2.30(3H, s), 2.42 (2H, q), 3.04(4H, t), 3.48(4H, t), 4.06 (2H, d), 4.28(2H, d), 4.36(1H, s), 6.97 (2H, m), 7.34(1H, s), 7.84(1H, s).	oil phase
146		1.22(3H, t), 2.29(3H, s), 2.37(2H, q), 3.13(4H, t), 3.41(4H, t), 3.56(2H, d), 4.27(4H, s), 6.90(3H, m), 7.04(5H, s), 7.25(5H, s).	oil phase
147		0.91(3H, s), 1.02(3H, s), 1.28(3H, t), 2.48(3H, s), 3.04(4H, t), 3.54(4H, t), 4.36(2H, q), 5.98(2H, d), 6.90(3H, m), 7.68(1H, s).	oil phase
148		1.14(3H, t, J=7.5Hz), 2.35(3H, s), 2.43 (2H, q, J=7.5Hz), 3.51(4H, t, J=4.6Hz), 3.90(4H, t, J=4.6Hz), 3.92(3H, s), 6.19 (1H, d), 7.21(2H, dd), 7.65(1H, m), 7.78 (1H, s).	158-159°C
149		1.09(3H, t, J=7.5Hz), 2.38(3H, s), 2.54 (2H, q, J=7.5Hz), 3.31(4H, t, J=5.0Hz), 3.63(4H, t, J=5.0Hz), 3.92(3H, s), 6.84 (1H, d), 6.96(2H, dd), 7.21(1H, d), 7.69 (1H, s).	198-199°C

Antitumor activities of the compounds of present invention were tested. Antitumor activities of compounds of the present invention were tested in vitro against 5 kinds of human tumor cell lines and 2 kinds of leukemia tumor cell lines. The method of in vitro test is as follows.

Example 1)

In vitro antitumor effect against human tumor cell lines

A. Tumor cell line : A549 (human non-small lung cell)
SKOV-3 (human ovarian)
HCT-15 (human colon)
XT 498 (human CNS)
SKMEL 2 (human melanoma)

B. Method of test(SRB Assay Method)

a. Human solid tumor cell lines, A594(non-small lung cell), SKMEL-2(melanoma), HCT-15(colon), SKOV-3(ovarian), XF-498(CNS) were cultured at 37℃, in 5% CO_2 incubater using the RPMI 1640 media containing 10% FBS, while they were transfer-cultured successively once or twice per week. Cell cultures were dissolved into the solution of 0.25% trypsin and 3 mM CDTA PBS(-) and then cells were separated from media which the cells were sticked on.

b. 5×10^3-2×10^4 cells were added into each well of 96-well plate and cultured in 5% CO_2 incubater, at 37℃, for 24 hours.

c. Each sample drugs was dissolved in a small quantity of DMSO, and diluted to concentrations prescribed in experiment with media, and then the final concentration of DMSO was controlled below 0.5%.

d. A medium of each well cultured for 24 hours as above b., was removed by aspiration. 200 μl of drug samples prepared in c. was added into each well and the wells were cultured for 48 hours. Tz(time zero) plates were collected at the point of time drugs were added.

e. After Tz plates and plates were treated with cell fixing by TCA of SRB assay method, staining of 0.4% SRB solution, washing with 1% acetic acid, OD values were measured at 520 nm, following elution of dye with 10 mM Tris solution.

C. Calculation of result

a. Time zero(Tz) value was determined by obtainment of SRB protein value at the point of time drugs were added.

b. Control value(C) was determined with OD value of well that was not added with drug.

c. Drug-treated test value(T) was determined with OD value of well treated with dug.

d. Drug effects of growth stimulation, net growth inhibition, net killing etc. were determined with Tz, C and T.

e. If $T \geq Tz$, cellular response function was calculated with $100x(T-Tz)/(C-Tz)$, and if $T < Tz$, with $100\times(T-Tz)/Tz$.

The results are shown in the next table.

* REFERENCE

1) P. Skehan, R. Strong, D Scudiero, A. Monks, J. B.Mcmahan, D.T. Vistica, J. Warren, H. Bokesh, S. Kenny and M. R. Boyd : Proc. Am. Assoc. Cancer Res., 30, 612(1989)

2) L.V. Rubinstein, R.H. Shoemarker, K. D. Paull, R.M. simon, S. Tosini, P. Skehan, D. Scudiero, A. Monks and M. R. boyd. ; J. Natl. Cancer Inst., 82, 1113(1990)

3) P. Skehan, r. strong, D. Scudiero, A. monks, J. B. Memahan, D. t. Vistica, J. Warren, H. Bokesh, S. Kenny and M. R. Boyd.;J. Natl. Cancer ins., 82. 1107(1990)

D. Results.

It was found that the compounds of present invention have the superior antitumor activities to those of the control, cisplatin against 5 kinds of human solid cancer cell lines. Especially, compounds of example 1), 6), 13), 16), 28), 29), 38), 41), 47), 48), 49), 50), 55), 61), 91), 97), 98), 100), 108), 109), 111), 113), 115), 118), 119), 120), 121), 126), 128), 129), 144), 148), 149) have superior antitumor activities to those of cisplatin.

EXAMPLE NUMBER	NET GROWTH AS% OF CONTROL (Conc. μg/mL)				
	A594	SK-OV-3	SK-MEL-2	XF-498	HCT-15
1	0.1372	0.0269	0.0172	0.1149	0.0479
6	0.0091	0.0072	0.0092	0.0156	0.0108
8	1.1428	0.3930	0.8302	1.2938	1.0499
13	0.2483	0.0697	0.1771	0.2769	0.0829
16	0.4491	0.0263	0.0182	0.1662	0.1160
18	1.0813	0.7207	0.8138	0.8275	0.6850
21	1.9952	1.0423	1.7609	2.8475	0.6684
22	2.2086	1.2588	1.8210	2.3352	0.6764
23	1.9836	0.5929	0.8665	2.2896	1.0053
28	0.5958	0.3192	0.6495	0.7663	0.3756
29	0.0002453	0.0001310	0.0007708	0.0001901	0.0007707
38	0.4266	0.0709	0.0833	0.2836	0.0652
41	0.4464	0.0836	0.0981	0.3818	0.0878
47	0.3693	0.2094	0.4384	0.4998	0.2975
48	0.0913	0.0583	0.0954	0.1430	0.0498
49	0.0917	0.0223	0.0723	0.0955	0.0946
50	0.0984	0.0732	0.0954	0.0736	0.0828
55	0.5074	0.1088	0.2812	0.4094	0.1577
60	2.8176	1.7486	0.6468	2.1795	0.3410
61	0.8539	0.1710	0.1594	0.4343	0.0910

EXAMPLE NUMBER	NET GROWTH AS% OF CONTROL (Conc. μg/mL)				
	A594	SK-OV-3	SK-MEL-2	XF-498	HCT-15
62	3.5875	0.2431	0.2894	1.1457	0.2950
91	0.5284	0.3156	0.5562	0.9176	0.5979
97	0.3518	0.0536	0.01778	0.2965	0.1489
98	0.3489	0.0645	0.1822	0.2229	0.1801
100	0.0016111	0.0015197	0.0032233	0.0020713	0.0065666
108	0.1158	0.0797	0.1277	0.1352	0.0741
109	0.1088	0.0832	0.1079	0.1494	0.0581
111	0.1611	0.0661	0.1258	0.0949	0.0749
113	0.4371	0.1680	0.3368	0.5967	0.0973
115	0.6168	0.2201	0.3672	1.4025	0.2081
118	0.0038	0.0011	0.0046	0.0042	0.0024
119	0.3824	0.1129	0.2414	0.5133	0.2026
120	0.0001299	0.0000226	0.0002677	0.0001193	0.0001265
121	0.0116039	0.0020599	0.0177227	0.0087927	0.0070088
126	0.006171	0.0005225	0.0110493	0.0048476	0.0058752
127	1.5462	0.4162	0.4776	1.3486	0.5366
128	0.0059411	0.0013953	0.0127665	0.0039702	0.0065951
129	0.0000119	0.0000033	0.0000389	0.0000117	0.0000384
144	1.0350	0.6289	0.6060	4.4550	0.4738
148	0.6767	0.3129	0.1582	0.7615	0.3203
149	0.3883	0.1819	0.1731	0.4255	0.0471
Cisplatin	0.8184	0.7134	0.7147	0.7771	3.0381

Example 2)

* In vitro antitumor effects against animal leukemia cells.

A. Material of experiment

Tumor cell lines : L1210(mouse leukemia cell)

P388 (mouse lymphoid neoplasma cell)

B. Method of experiment(Dye Exclusion Assay)

1) L1210 and P388 cells that were cultured in RPMI 1640 media containing 10 % FBS were regulated as the cell concentration of 1×10^6 cells/ml.

2) Sample drugs diluted with log dose were added into the cells, and it were cultured at 37℃, for 48 hours, in 50 % CO_2 incubater, and then viable cell number was measured, Viable cell number was measured with dye exclusion test using trypan blue.

3) The concentration of sample compounds of 50 % cell growth inhibition compared with standard group was determined as IC_{50}. The results are shown at the next table.

* REFERENCE

1) P.Skehan, R. Strong, D. Scudiero, A. Monks, J. B. Mcmahan, D. T. Vistica,

J. Warren, H. Bokesh, s. Kenney and M. R. Boyd. : Proc. Am. Assoc. Cancer

Res., 30, 612(1989).

2) L.V.Rubinstein, R.H.Shoemaker, K.D Paull, R.M. Simon, s. Tosini,P.Skehan,

D. Scudiero, A. Monks, J. Natl. Cancer Inst., 82, 1113(1990)

3) P.Skehan, R. Strong, D.Scudiero, J. B. Mcmanhan, D.T. Vistica, J. Warren,

H. Bokesch, S.Kenney and M.R. Boyd. : J. Natl. Cancer Inst., 82, 1107(1990)

C. Result

As the results of measurement of antitumor activities of compounds of the present invention against L1210 and P388 mouse cancer cells, it was found that compouds of example 1), 6), 13), 16), 29), 38), 41), 47), 48), 49), 108), 118), 120), 128), 148), 149) had same or more excellent antitumor activities than those of the control drug, mytomicin C.

EXAMPLE NUMBER	ED_{50} ($\mu g/mL$)	
	L1210	P388
1	1.6	0.6
6	0.6	0.3
13	1.7	1.6
16	1.8	1.6
29	0.4	0.5
38	1.4	1.0
41	1.4	2.0
47	0.3	0.3
48	1.9	1.8
49	1.3	0.6
50	2.0	1.5
97	2.0	1.6
98	2.0	2.1

EXAMPLE NUMBER	ED_{50} ($\mu g/mL$)	
	L1210	P388
108	0.8	0.9
118	0.06	0.06
119	2.2	2.0
120	0.3	0.1
128	0.5	0.2
148	1.5	1.3
149	0.9	1.6
mitomycin C	1.6	1.1

In vivo antitumor activity test was carried out in mice with samples having significance in in vitro test.

Example 3)

* In vivo antitumor effects against mouse leukemia P388 cells.

A. Material of experiment

BDFI mice were used.

B. Method of experiment

1) Leukemia P388 cells being transfer-cultured succesively in DBA/2 mouse, were grafted i.p. into each mouse of a group comprising 8 mice of 6 week old BDFI mouse as the dose of 1×10^6cells/ 0.1 ml.

2) Sample drugs were dissolved in PBS or suspended in 0.5% Tween 80, and then injected into abdominal cavity of mouse at each prescribed concentration on days 1, 5, 9, respectively.

3) With observation every day, survival times of tested mice were measured. Antitumor activities was determined in such a manner that the increasing ratio(T/C%) of average survival days of drug-treated groups compared with the control group was calculated using the mean survival times of each tested groups.

The results are shown at the next table.

* REFERENCE

A. Goldin, J. M. Venditti, J. S. Macdonald, F.M.Muggia, J.E.Henney and V. T. DeVita. :Euro. J. S. Macdonald, F. M. Muggia, J. E. Henney and V. T.

DeVita: Euro. J. Cancer, 17, 129 (1981).

* Experimental Conditions for mouse P388

Animal	: BDFI mouse (8 mice/ group)
Tumor	: mouse P388
Inoculum size	: 10^6 cells/mouse
Inoculum site	: i. p.
Treatment site	: i. p.
Treatment time	: days 1, 5, 9
Parameter	: median survival time
Criteria	: T/C %

C. Result

Through in vivo experiment using P388 mouse cancer cells, significant antitumor effect of the compounds of example 1), 6), 16), 29) were observed.

Example No.	Dose (mg/kg)	T/C(%)	etc.
1	100	134.6	
	50	109.1	
6	100	183.3	
	50	133.3	
16	100	131.8	
	50	113.6	
29	100	190.9	
	50	136.4	

Example 4)

* In vivo antitumor activities against mouse solid tumor, B16 melanoma.

A. Material of experiment.

BDF1 mouse was used in experiment while being successively transfer-cultured in C57BL/6 mice by s.c.

B. Methods

1) After 1g of tumor was added into cold balanced salt solution up to be 10ml,

it was homogenized (10:1,brei).

2) 0.5 ml Brei of the above 1) were grafted into each BDF1 mouse by i. p.

3) Median survival time was measured, and the activity was determined in such a manner that if T/C was over 125 %, it presented moderate activity, while if it is over 150. %, it had significant activity.

The results are shown at the next table.

*REFERENCE

A. Goldin, J. M. Venditti, J. S. Macdonald, F. M. Muggia, J.E.Henney and V. T. DeVita, Euro.J.Cancer, 17, 129(1981).

* Experimental Conditions for Mouse B16 melanoma.

Animal	:BDFI mouse (8 mice /group)
Inoculum size	:10^5 cells/mouse
Inoculum site	:i. p.
Treatment site	:i. p.
Treatment time	:days 1, 5, 9
Parameter	:median survival time
Criteria	:T/C %

C. Results

With in vivo experiment using B16 mouse melanoma solid tumor, it was observed that the compounds of examples 6), 16) etc. have the significant antimumor activities.

Example No.	Dose	T/C(%)	Etc.
6	200	139.4	
	100	124.2	
	50	127.3	
16	200	118.2	
	100	127.3	
	50	115.2	

Example 5)

* Acute toxicity test (LD_{50}) : Litchfield-Wilcoxon method.

6 week old ICR mice(male 30±2.0g) was fed freely with solid feed and water at room temperature, 23±1℃ and at humidity 60±5%. Sample drugs were injected into the abdominal cavities of mice, while each goup comprises 6 mice.

Oserved during 14 days, external appearances and life or dead were recorded, and then, visible pathogenies were observed from dead animals by dissection. LD_{50} value was calculated by Litchfiled-wilcoxon method.

The results are shown at the next table.

Example No.	LD_{50}(mg/ml)	
	i.p.	p.o.
6	248.5	>622
28	>1,800	>2,000
61	>1,687	
97	1,100	
98	>1,800	>2,000
108	>2,000	>3,110
109	2,000	>2,073
118	182.8	571.8
148	425.3	
149	410.5	
cisplatin	21.4	

As described above, it was found that the compouds of the present invention are more safer and have superior antitumor activities to cisplatin, and accordingly have solved the problems of drugs by the prior art such as restriction of dosage, toxicity, etc.

Examples of pharmaceutical preparations

Tablets: (examples 1-4)

Tablet(250mg) was prepared with the ingredients of the following table by conventional tablet manufacturing method.

Examples	ingredients(mg)	
1	compound of example 1	20
	lactose	120
	microcrystalline cellulose	30
	corn starch	40
	povidone	30
	sodium starch glycolate	8
	magnesium stereate	2
2	compound of example 148	20

		lactose	110
		microcrystalline cellulose	40
		corn starch	45
		povidone	25
		sodium starch glycolate	8
		magnesium stearate	2
	3	compound of example 16	20
		lactose	120
		microcrystalline cellulose	35
		corn starch	35
		povidone	30
		sodium starch glycolate	8
		magnesium stearate	2
	4	compound of example 149	20
		lactose	100
		microcrystalline cellulose	45
		corn starch	50
		povidone	25
		sodium starch glycolate	8
		magnesium stearate	2

Capsules(example 5-8)

Capsule(250mg) was prepared with the ingredients of the following table by conventional capsule manufacturing method.

Examples	ingredients(mg)	
5	compound of example 1	10
	lactose	100
	corn starch	100
	povidone	30
	sodium starch glycolate	7
	magnesium stearate	3
6	compound of example 148	10
	lactose	105

		corn starch	100
		povidone	25
		sodium starch glycolate	7
		magnesium stearate	3
	7	compound of example 16	10
		lactose	90
		corn starch	110
		povidone	30
		sodium starch glycolate	7
		magnesium stearate	3
	8	compound of example 149	10
		lactose	95
		corn starch	110
		povidone	25
		sodium starch glycolate	7
		magnesium stearate	3

Injectable preparations (examples 9 - 16)

Injectable preparations(5ml of ampoule and vial) were prepared with the ingredients of the following tables by the conventional injection manufacturing method.

Examples (ampoule)	ingredients	
9	compound of example 1	30mg
	polyoxy 35 castor oil	4000mg
	absolute ethanol	1.17ml
	distilled water for inj.	q.s.
10	compound of example 148	30mg
	polyoxy 35 castor oil	3200mg
	absolute ethanol	1.97ml
	distilled water for inj.	q.s.
11	compound of example 16	30mg
	polyoxy 35 castor oil	3500mg

	absolute ethanol	1.68ml
	distilled water for inj.	q.s.
12	compound of example 149	30mg
	polyoxy 35 castor oil	3000mg
	absolute ethanol	2.16ml
	distilled water for inj.	q.s.
Example 13(vial)	compound of example 1	30mg
	polyoxy 35 castor oil	4000mg
	absolute ethanol	1.17ml
	distilled water for inj.	q.s.
14	compound of example 148	30mg
	polyoxy 35 castor oil	3200mg
	absolute ethanol	1.97ml
	distilled water for inj.	q.s.
15	compound of example 16	30mg
	polyoxy 35 castor oil	3500mg
	absolute ethanol	1.68ml
	distilled water for inj.	q.s.
16	compound of example 149	30mg
	polyoxy 35 castor oil	3000mg
	absolute ethanol	2.16ml
	distilled water for inj.	q.s.

Ointment(examples 17 - 20)

Ointment(1g) was prepared with the ingredients of the following table by the conventional ointment manufacturing method.

Examples	ingredients(mg)	
17	compound of example 1	6
	polyoxy 40 hydrogenated castor oil	350
	absolute ethanol	100
	sodium p-oxybenzoate	1.5

		NaH_2PO_4	1.06
		citric acid	1.48
		propyleneglycol	200
		glycerine	150
		cetostearyl alcohol	50
		cetiol H. E.	130
		purified water	q.s.
	18	compound of example 148	6
		polyoxy 40 hydrogenated castor oil	300
		absolute ethanol	100
		sodium p-oxybenzoate	1.5
		NaH_2PO_4	1.06
		citric acid	1.48
		propyleneglycol	200
		glycerine	150
		cetostearyl alcohol	50
		cetiol H. E.	145
		purified water	q.s.
	19	compound of example 16	6
		polyoxy 40 hydrogenated castor oil	350
		absolute ethanol	150
		sodium p-oxybenzoate	1.5
		NaH_2PO_4	1.06
		citric acid	1.48
		propyleneglycol	150
		glycerine	150
		cetostearyl alcohol	100
		cetiol H. E.	135
		purified water	q.s.
	20	compound of example 149	6
		polyoxy 40 hydrogenated castor oil	300
		absolute ethanol	100
		sodium p oxybenzoate	1.5
		NaH_2PO_4	1.06

	citric acid	1.48
	propyleneglycol	200
	glycerine	100
	cetostearyl alcohol	100
	cetiol H. E.	147
	purified water	q.s.

Suppository(examples 21-24)

Suppository(1g) was prepared with the ingredients of the following table by conventional suppository manufacturing method.

Example	ingredients(mg)	
21	compound of example 1	6
	polyoxy 35 castor oil	250
	glycerine	80
	propyleneglycol	50
	stearyl alcohol	50
	stearic acid	50
	Witepsol®	364
	glycerylmonostearate	150
22	compound of example 148	6
	polyoxy 35 castor oil	230
	glycerine	80
	propyleneglycol	70
	stearyl alcohol	50
	stearic acid	50
	Witepsol®	414
	glycerylmonostearate	100
23	compound of example 16	6
	polyoxy 35 castor oil	245
	glycerine	80
	propyleneglycol	65
	stearyl alcohol	70
	stearic acid	60
	Witepsol®	394

	glycerylmonostearate	80
24	compound of example 149	6
	polyoxy 35 castor oil	225
	glycerine	70
	propyleneglycol	60
	stearyl alcohol	55
	stearic acid	50
	Witepsol®	459
	glycerylmonostearate	75

Oral solution(example 25-28)

Oral solution(100ml) was prepared with the ingredients of the following tables by the conventional oral solution manufacturing method.

Example	ingredients	
25	compound of example 1	30mg
	polyoxy 40 hydrogenated castor oil	30g
	absolute ethanol	2ml
	propyleneglycol	15g
	polyethyleneglycol 400	10g
	Tween 80	5g
	methy p-oxybenzoate	0.1g
	purified sugar	12g
	herb perfume	0.1mg
	purified water	q.s.
26	compound of example 148	30mg
	polyoxy 35 castor oil	30g
	absolute ethanol	2ml
	propyleneglycol	12g
	polyethyleneglycol	15g
	Tween 80	10g
	methyl p-oxybenzoate	0.1g
	purified sugar	12g
	herb perfume	0.1ml
	purified water	q.s.

27	compound of example 16	30mg
	polyoxy 35 castor oil	25g
	absolute ethanol	2ml
	propyleneglycol	20g
	polyethyleneglycol 400	15g
	Tween 80	7g
	methyl p-oxybenzoate	0.1g
	purified sugar	15g
	herb perfume	0.15ml
	purified water	q.s.
28	compound of example 149	30mg
	polyoxy 35 castor oil	30g
	absolute ethanol	2ml
	propyleneglycol	17g
	polyethyleneglycol 400	12g
	Tween 80	10g
	methyl p-oxybenzoate	0.1g
	purified sugar	13g
	herb perfume	0.15ml
	purified water	q.s.

Troche(examples 29-32)

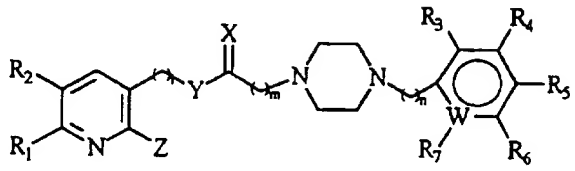
Troche(500mg) was prepared with the ingredients of the following table by conventional troche manufacturing method.

Example	ingredients(mg)	
29	compound of example 1	20
	mannitol	300
	sugar	100
	corn starch	40
	povidone	30
	sodium starch glycolate	8
	magnesium stearate	2
30	compound of example 148	20

		mannitol	280
		sugar	120
		corn starch	45
		povidone	25
		sodium starch glycolate	8
		magnesium stearate	2
	31	compound of example 16	20
		mannitol	320
		sugar	100
		corn starch	20
		povidone	30
		sodium starch glycolate	8
		magnesium stearate	2
	32	compound of example 149	20
		mannitol	300
		sugar	110
		corn starch	50
		povidone	10
		sodium starch glycolate	8
		magnesium stearate	2

What is claimed is :

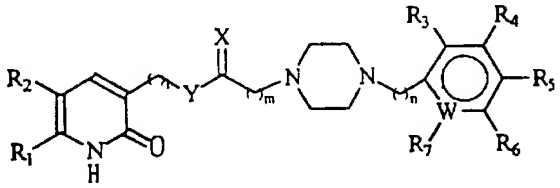
1. A compound of the general formula(I) and pharmaceutically acceptable acid addition salt thereof.



(I)

wherein R_1 and R_2 are indenpendently hydogen, C_1-C_6 alkyl or optionally substituted C_3-C_6 membered cycloalkyl containing C_3-C_8; R_3, R_4, R_5, R_6 and R_7 are independently hydrogen, halogen, hydroxy, nitro, C_1-C_4 lower ester, C_1-C_4 lower alkyl, C_1-C_4 lower alkoxy, aryl, arylalkoxy or unsaturated amine; l is an integer of 0-7; m and n are independently an integer of 0-1; W is carbon or nitrogen; X is oxygen, sulfur, optionally substuted imine; Y is nitrogen or oxygen; and Z is hydrogen, C_1-C_8 alkoxy, aryloxy, C_1-C_4 alkylamine, cycloamine containing N_1-N_5 or oxo group.

2. A compound of the general formula (I') as claimed in claim 1, wherein Z is oxo group,

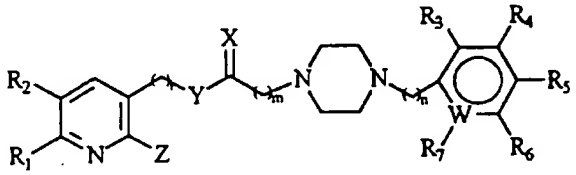


(I')

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, l, m, n, W, X and Y are the same with those in the claim 1 and pharmaceutically acceptable acid addition thereof.

3. A pharmaceutical composition comprising a compound of the general

formula (I) or acid addition salt thereof as active ingredient and one or more conventional adjuvants selected from the group consisting of conventional vehicles, binding agent, degrading agent, lubricating agent, dissolving agent, aids for dissolution, stabilizing agent, base of ointment, pH-adjusting agent, perfume or the like.



(I)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, l, m, n, W, X, Y and Z are the same with those in the claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 96/00005

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 213/65, 213/32, 213/14; A 61 K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 213/00; A 61 K 31/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chemical Abstracts

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel DARC, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 March 1996 (22.03.96)	03 May 1996 (03.05.96)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Hammer Telephone No. 1/5337058/44

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 96/00005

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT
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International application No.
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